Original Communications

THE LIMITATIONS AND DANGERS OF THE INTRAUTERINE APPLICATION OF RADIUM IN THE TREATMENT OF CARCINOMA OF THE BODY OF THE UTERUS*

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IT WELL may seem presumptuous that I, with relatively little experience with radium in the treatment of carcinoma of the body of the uterus, should attempt to write a paper on its limitations and dangers. On the other hand, for many years I have been greatly interested in the clinical and laboratory study of carcinoma in this situation, especially its ways of invasion and dissemination with their resulting conditions. In these studies I was impelled not only by an inherent curiosity to learn all I could about its life history but also by the desire to ascertain the most effective form of treatment. From these observations I would expect that in many cases intrauterine radium, if wisely applied, would be in close proximity to all of the carcinoma present. In other instances the intimate application of radium to all of the growth would be a matter of chance, and in still others it would be impossible. Irrespective of the radiosensitivity of a given carcinoma of the body of the uterus, its curability by radium must, in a large measure, depend on the proximity of the entire growth to the radium in the uterine cavity. The closer this proximity the greater the chance for a cure, especially in radio-resistant tumors. It is the purpose of this paper to present the conditions observed in individual cases of carcinoma of the body of the uterus from the standpoint of the intimate intrauterine application

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of radium to all portions of the growth. I also desire to report some of the unfortunate results of this remarkable therapeutic agent which I have encountered.

Burnam and Healy, as a result of their interest and also their experience in the treatment of carcinoma of the body of the uterus both by surgery and by radiation therapy, are in an excellent position to estimate the relative value of these two procedures. In 1928, Burnam[1] called attention to the fact that the majority of these tumors are of low-grade malignancy and therefore well suited for good operative results and ill suited for radium treatment because he believed that they were very radioresistant. In addition to the factor of radiosensitivity, it is clinically impossible to determine the exact extent of such growths to know whether only a part or the entire endometrium is involved, and to know the depth of the invasion of the uterine wall if the latter is present. ''By reason of this lack of diagnostic precision, accuracy in dosage is impossible. . . . To summarize, the indication for radium treatment in body cancer is inoperability by reason of general or local causes.''

Later as a result of his own experience, as well as that of others in the treatment of carcinoma of the body of the uterus with intrauterine radium, he made the following statements in a paper published by him in 1931.[2] ''In operable cancers of the body of the uterus, radium offers a method of treatment comparable to the best surgical treatment in its permanent results. . . . It obviates to a large measure, at least, primary mortality and is applicable to a large number of patients who are bad surgical risks. . . . Radiation offers a possibility of cure in a considerable percentage of inoperable and recurrent cancer of the body of the uterus. . . . Preoperative radiation does not increase the hazards of operation and postoperative radiation would seem to be a logical procedure in many cases.''

Burnam,[3] writing in 1933, was still enthusiastic over the surprisingly good results of radiotherapy alone in these cases. On the other hand he states: ''Surgical removal and postoperative radiation is the method of choice in operable cases in good general condition. . . . Inoperable, recurrent and cases with local operable conditions but general complicating factors rendering operation hazardous should be treated by ray therapy alone.'' In his presentation of the technic of radiation therapy in carcinoma of the body of the uterus he states: ''In operable cases our own feeling is that chief reliance should be placed on the intrauterine radium; and the external radiation whether by teleradium or x-ray should be a supplementary procedure.'' His patients, thus treated, return in from six to ten weeks for a check-up and another curettage is performed. If cancer is found, the patient is preferably operated upon. If this is hazardous, a second radium treatment is employed.

Healy and Cutler,[4] in a paper published in 1930 on the comparative results of radiation and operation in the treatment of carcinoma of the body of the uterus, demonstrated that the results of radiation alone in the operable cases compare favorably with the best surgical statistics. They state: ''The decision between radiation and operation in operable fundus carcinoma must for the present depend on the circumstances in each individual case taking into account such factors as histologic type, technical operability, stage of disease, general or constitutional and local complications.''

In 1933, Healy[5] makes the following statement: ''A diagnosis of cancer of the corpus should, in general, be regarded as an indication for complete hysterectomy.'' He advises that radium capsules be placed in the uterine and cervical canals at the termination of a diagnostic curettage in all patients at or beyond the menopause. He also suggests that it would be well to precede the diagnostic curettage by the

application of deep x-rays in order to diminish the chance of causing metastases by the curettage. He again calls attention to the surprisingly good results of radiation in the treatment of carcinoma of the body of the uterus, and, therefore, its great value in all operable cases in which operation is contraindicated because of some associated condition. In a later paper, also published in 1933, Healy[6] states: "For somewhat more than two years the routine procedure in cancer of the corpus cases at the Memorial Hospital has been to treat them with radium at the time of the diagnostic curettage and to follow this with high voltage x-ray unless the patient is extremely corpulent. Six to eight weeks later in all operable cases abdominal hysterectomy has been done. . . . Two interesting observations have been made, first, the hysterectomy has not been made more difficult because of the preoperative radiation; second, very little viable cancer and in more than half of the cases no cancer at all could be found in the uterus on microscopic examination after its removal."

At the last meeting of the American Gynecological Society, Healy[7] presented his results in the treatment of carcinoma of the body of the uterus by radiation alone and by radiation combined with hysterectomy. The results of both forms of treatment in all grades of corpus carcinoma were excellent. "The end-results obtained in patients with adenocarcinoma of the corpus treated by radiation alone were superior to those resulting when hysterectomy was combined with radiation." In closing the discussion of his paper he stated[8]: "Adenocarcinoma of the corpus is going out of the hysterectomy class into the radiation class; and, on the other hand, if you feel that it is such a favorable case for operation that you must do a hysterectomy, then the patient should be given the benefit of preoperative irradiation both within the uterus with radium and around the entire pelvic cavity with roentgen rays."

If the results of radiation therapy alone in operable cases compare favorably with the best surgical statistics and may excel these in the histologically more malignant grades of corpus carcinomas, it might be inferred that it should take preference over surgery in the treatment of all corpus carcinomas. Since the pendulum apparently is swinging from surgery toward radiation therapy in the treatment of this disease, it might be well to pause and consider some of the possible limitations of radiation therapy.

THE PROBLEM

Approximately 80 per cent of the patients with carcinoma of the body of the uterus are past the menopause, and many are over sixty years of age. (Wallingford[9] recently showed that 80 per cent of 183 patients with this disease cared for on the gynecologic service of the Albany Hospital were over fifty years of age. Smith[10] and also Beattie[11] recently published a like age incidence.) Old age, in itself, is often not a contraindication for a major operation. However, it is more apt to be associated with obesity and serious organic diseases than less advanced years. Hysterectomy for carcinoma of the body of the uterus in an obese, elderly nulliparous woman is technically difficult. Serious organic diseases also increase the dangers of an operation. Unfortunately these form a large group of the patients with corpus carcinoma.

The situation of the carcinoma in the uterus and the extent of its invasion and dissemination as found in operative cases varies greatly. In some the greater portion or even the entire uterine mucosa is replaced by the growth so that it is impossible to determine the exact site of its origin (Figs.1 and 2). In others only a small area of the mucosa is involved thus indicating the approximate starting place of the carcinoma (Figs. 3, 4, 5 and 6). This may occur in any portion of the endometrium. Sometimes the growth is very superficial, involving only the mucosa, so that it may be entirely removed by curettage. I have seen a few instances where typical carcinoma was present in the curettings but none was found in the uterus after its removal. Unfortunately the growth frequently has invaded the uterine wall and may even have extended to other structures when the diagnosis is made. These variations in the situation of the carcinoma and the degree of its invasion,
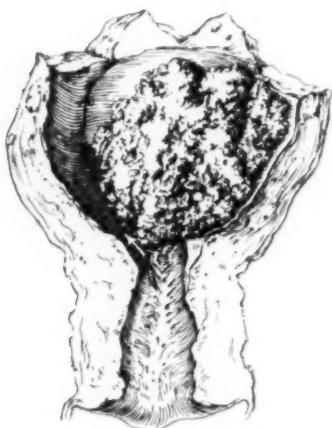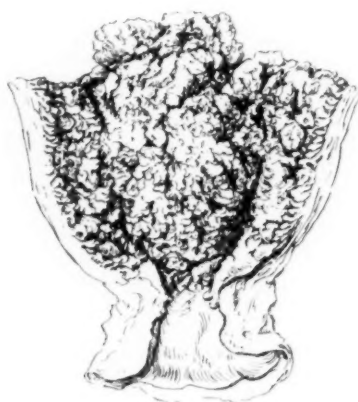
Fig. 1.   Fig. 2.

Fig. 1.—Papillary carcinoma replacing nearly half of the uterine mucosa. (×½). Capsules of radium, tandem formation, would be likely to occupy the portion of the uterine cavity lateral to the tumor (see arrows) and therefore would not be in close proximity to the entire growth. The drawing was made several years ago. Unfortunately the patient's name or hospital number was not attached.

Fig 2.—Papillary carcinoma replacing the entire uterine mucosa with slight invasion of the uterine wall (×½). Patient (A. H. No. 174-32), aged fifty-four years, menopause at the age of forty-eight, bleeding of three years' duration, at times profuse. The inability in any case to determine the exact situation of the carcinoma, the amount of mucosa involved, as well as the invasion of the uterine wall and depth of the latter makes the intimate application of intrauterine radium to any or all of the growth a matter of chance. This chance is lessened if the capsules of radium are so placed as to cover the mucosa of the entire uterine cavity.

which can be realized only by the laboratory study of the ovaries, tubes, and uterus, often make the intimate application of the radium to all of the growth a matter of chance or even impossible.

The duration of symptoms as an index of the extent of the disease is often misleading. In some patients with a history of abnormal bleeding of long duration a small superficial papillary growth may be found, or even if the entire mucosa has been replaced by carcinoma, there may be little or no invasion of the uterine wall. In other patients with a history

of bleeding of short duration the uterine wall may be deeply invaded by the growth. This may have extended to adjacent structures; secondary carcinomas may be present in the tubes and ovaries, and metastases to more distant structures may have occurred.

A bimanual pelvic examination will reveal the size of the uterus and its appendages and usually enables us to determine whether or not they
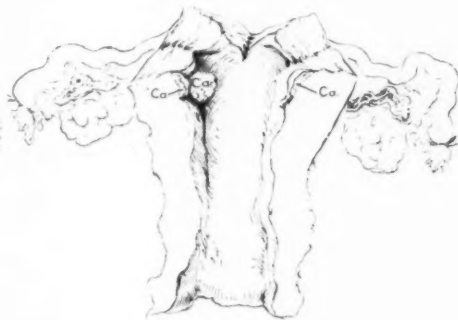

Fig. 3.   Fig. 4.

Fig. 3.—Early superficial carcinoma of the mucosa of the posterior wall of the uterus ($\times\frac{1}{2}$). Patient (A. H. No. 1305-31), aged seventy-two years, menopause at the age of fifty, bleeding of five months' duration, at times very profuse. The carcinoma is so superficial that it might be removed by curettage. Radium reaching the fundus of the uterus would be in close proximity to the entire growth.

Fig. 4.—Early superficial carcinoma of the mucosa of the right uterine cornu and anterior wall ($\times\frac{1}{2}$). Patient (A. H. No. 8245-33), aged forty-five years, menopause at the age of forty-two, irregular scanty bleeding of five months' duration. The uterine cavity is narrow and of the triangular type. Radium reaching the fundus of the uterus would be in close proximity to the entire growth. Unfortunately the only accurate means of ascertaining if a given carcinoma is easily accessible to intrauterine radium is by the operative removal of the ovaries, tubes, and uterus and their laboratory study.
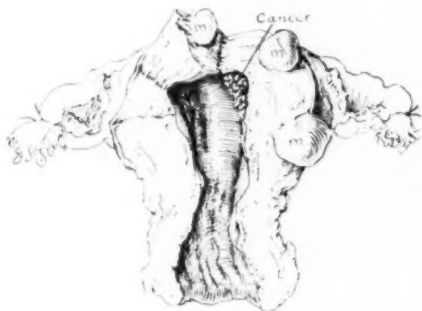
Fig. 5.   Fig. 6.

Fig. 5.—Early superficial carcinoma of the mucosa of the left uterine cornu, not extending into the uterine ostium of the tube; multiple small myomas ($\times\frac{1}{2}$). Patient (A. H. No. 2247-33), aged fifty-three years, menopause at the age of forty-eight, bleeding slight and of only three months' duration. The uterine cavity is small and of the triangular type. Radium reaching the fundus of the uterus would be in close proximity to the entire growth. Carcinoma may arise in the mucosa of the isthmus of the uterus as well as in that of the fundus. Hence the reason for placing the capsules of radium so that they will extend from the fundus well into the cervical canal.

Fig. 6.—Early superficial carcinoma of the mucosa of the left uterine cornu extending through the uterine ostium of the tube into its uterine portion (see Fig. 29 of previous paper[13]) ($\times\frac{1}{2}$). Patient (A. H. No. 62-33), aged fifty-six years, menopause at the age of forty-one, occasional spotting of six months' duration. The uterine cavity is small but of the "Y" or bicornuate type. Radium reaching the fundus of the uterus might readily occupy the right cornu (see Fig. 7, b) and therefore might not be in close proximity to the carcinoma which has invaded the lumen of the uterine portion of the left tube. Hence the reason for placing a capsule of radium in both cornua.

are adherent. Enlarged and adherent pelvic organs may have resulted from causes other than carcinoma, and the latter may be present in pelvic structures which are normal on palpation. Vaginal metastases are readily detected and frequently, but not always indicate metastases in other situations.

A diagnostic curettage usually will enable one to ascertain whether or not carcinoma of the body of the uterus is present. This valuable diagnostic procedure is not infallible. Conditions sometimes are present which may render the detection of the growth by the curette and small ovum forceps very difficult. I found carcinoma in four uteri, removed by operation, in which a diagnostic curettage had failed to obtain some of the tumor. In three of these cases I had made the preliminary curettage. Two of these were associated with a submucous myoma. I also recall other instances where I had nearly missed the carcinoma. The conditions, which in my experience have contributed to the difficulties of a curettage in patients with carcinoma of the body of the uterus, have been:

1. Inaccessible uterine cavities in obese elderly nulliparous women and in elongation of the supravaginal portion of the cervix in uteri which had been sutured in the abdominal wall. (I have never encountered an instance of carcinoma developing in the body of the uterus after an interposition operation.)

2. Small growths in a large uterus, in a sharply flexed uterus, or in one cornu of a uterine cavity of the ''Y'' type.

3. A local infiltrating type of cancer with very little of the growth presenting in the uterine cavity.

4. Associated submucous myomas.

The surgeon is sometimes surprised and chagrined, on incising a uterus which he had thoroughly curetted prior to the hysterectomy, to find out what had been missed by the curette.

By means of the curette and especially small ovum forceps we are sometimes able to determine the approximate situation of the carcinoma. At other times as shown by examining the uterus after its removal, this diagnostic procedure had failed.

Since more than one histologic type or phase of the growth may be present in one uterus, the microscopic examination of tissue obtained by curettage may fail to disclose all types present and therefore prevent one from judging the sensitivity of the entire tumor to radium. This fallacy has recently been emphasized by Beattie.[11]

The difficulties and uncertainties of an exact pretreatment diagnosis in carcinoma of the body of the uterus constitute a greater handicap in the effective application of radium than in an operation.

THE ATTEMPTED SOLUTION OF THE PROBLEM

The study of the clinical course of these patients after operation without radiation, with radiation only, and with combined radiation

and operation, is of great value in ascertaining the percentage of clinical cures by these methods. It also is of assistance in determining the types of cases best adapted to each form of treatment. This phase of the problem has been well presented by Healy. On the other hand, it rarely discloses the reasons for the failures.

The laboratory study of material obtained at operation and autopsy from patients with untreated carcinomas is of great scientific value in ascertaining the natural course of the disease. It also should be of great assistance in indicating the form of treatment best suited to individual cases. The results of a similar study of material obtained from patients who have had a previous hysterectomy or radium treatment should assist us in determining two equally important questions; first, in what way these procedures may have failed to check the disease and, second, if they may have contributed to the dissemination of the growth. We may learn from such observations the causes of these unfortunate results and what might have been done to prevent them.

The primary morbidity and mortality associated with the use of radium are so slight, compared with those of operation, that it would be the ideal form of routine treatment if the ultimate results were as good as operation in all groups of cases. If intrauterine radium is to be curative in any case, the entire growth must be accessible to it. It is obvious that radium will be effective for a greater distance in radio-sensitive than in radioresistant tumors.

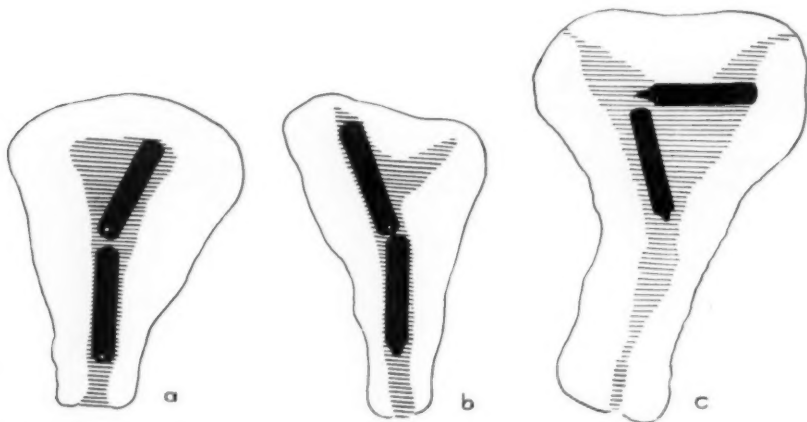### THE INFLUENCE OF THE NORMAL VARIATIONS IN THE SIZE AND SHAPE OF THE UTERINE CAVITY ON THE INTIMATE APPLICATION OF RADIUM TO CARCINOMA OF THE BODY OF THE UTERUS

We usually can determine the size of the uterus and the length of its cavity prior to the introduction of the radium. The same amount of radium would be more intimately applied to all of the growth in a uterus with a small cavity than in one with a large cavity, the situation and extent of the growth being similar in both instances.

It is impossible to ascertain the shape of the uterine cavity. It is obvious that radium would be more effectively placed in a uterine cavity of the triangular type than in one of the ''Y'' or bicornuate type should cancer be present in one or both uterine cornua.

In order to demonstrate the relation of the capsules of radium introduced in the uterine cavity to carcinoma actually or possibly present, the following studies were made with the assistance of Dr. Arthur J. Wallingford. The cavities of uteri removed at operation were filled with a 20 per cent solution of sodium iodide by means of a syringe inserted in the cervical canal. Capsules (without radium) were introduced through the cervix into the uterine cavity as they would be placed in the treatment of carcinoma of the body of the uterus. The cervix was

clamped and the specimen washed in order to remove any of the sodium iodide solution on its surface. Through the cooperation of Dr. William P. Howard, head of the x-ray department of the Albany Hospital, skiagrams were made of these specimens.

In one series of cases two or three capsules, in tandem formation in a fountain pen rubber, were introduced into the uterine cavity simulating a method frequently employed in the radium treatment of uterine conditions including carcinoma of its body (Fig. 7).

In a second series an attempt was made to first place a capsule with a wire soldered on one end into each uterine cornu, as employed in the Marie Curie Hospital; then other capsules (sometimes in tandem formation and at other times singly) were introduced into the uterine cavity between the capsules in the uterine cornua (Fig. 8).

Fig. 7.—The influence of the normal variations in the size and shape of the uterine cavity on the intimate application of radium to all portions of the uterine mucosa. Tracings of skiagrams of three uteri, into the cavities of which a solution of sodium iodide has been injected through the cervix; and two capsules, in a rubber tube in tandem formation, have been introduced as in the radium treatment of carcinoma of the body of the uterus ($\times\frac{1}{2}$). In uterus *a* the cavity is small and of the triangular type; the capsules would be in close proximity to carcinoma of any portion of the entire mucosa. In uterus *b* the cavity is of the "Y" type but fortunately is small. In uterus *c* the cavity is also of the "Y" type, but larger than the preceding one. The first capsule might have reached one cornu leaving the other unexposed. In this instance, however, it evidently struck the septum between the two cornua and was turned back into the uterine cavity. Capsules in single tandem formation cannot reach all portions of a uterine cavity of the "Y" type. Carcinoma is frequently situated in one or both uterine cornua. The type of uterine cavity as well as the exact situation of the carcinoma can be ascertained only by the removal of the uterus.

In a third series capsules were packed into the uterine cavity in an attempt to simulate the method illustrated by Burnam[3] in treating carcinoma of the body of the uterus with radium.

Carcinoma of the body of the uterus was present in 17 instances. The remaining 109 uteri may be divided into two groups:

1. Normal uterine cavities, 46.

2. Uterine cavities enlarged by intramural uterine myomas or distorted by submucous myomas and large polyps, 63. This latter group will be considered later.
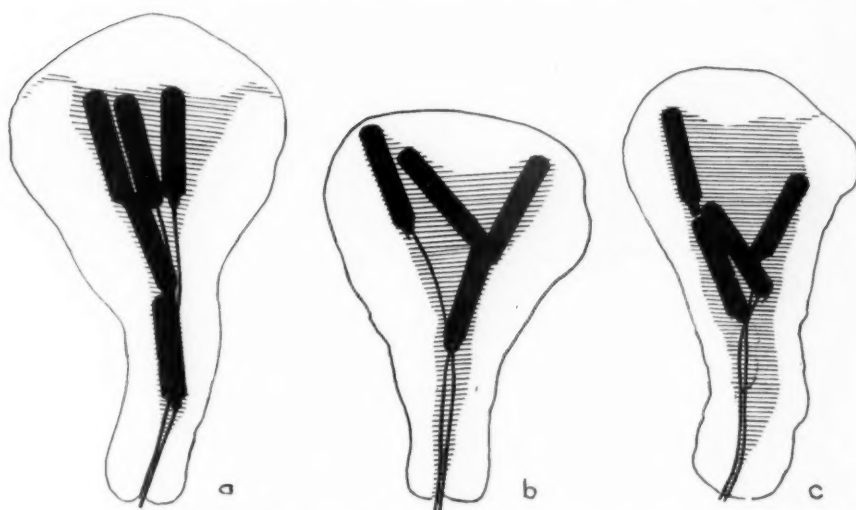
Fig. 8.—Tracings of skiagrams of three uteri in which an attempt was made to first place a capsule, with wire attached, in each cornu and between these two or three capsules, tandem formation, so that they would extend from the fundus well into the cervical canal ($\times \frac{1}{2}$). In uterus *a* although the capsules cover the entire mucosa much better than three capsules in tandem formation, the capsule intended for one cornu either failed to reach its destination or later became displaced. In uterus *b* with a cavity of the "Y" type a capsule is well placed in each cornu. In uterus *c* the capsules either failed to reach their destinations or subsequently became displaced. In all but small uterine cavities of the triangular type the placing of a capsule in each cornu and additional capsules between them will cover the entire mucosa better than two or three capsules in single tandem formation. Since failures in properly placing the capsules may occur when they are introduced in uteri after hysterectomy, it would seem that similar failures would occur more frequently in uteri which had not been removed.
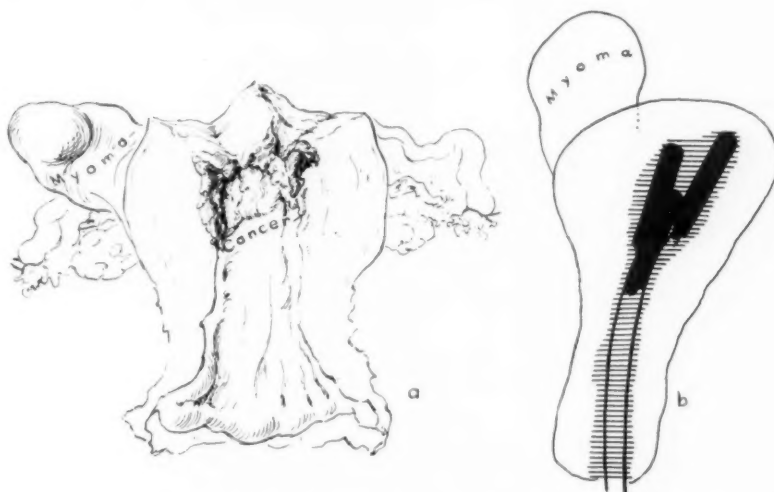
Fig. 9.—Carcinoma replacing the mucosa of the fundus with invasion of the uterine wall ($\times \frac{1}{2}$). Patient (A. H. No. 7907-33), aged forty-one years, menstruation regular and normal, slight bleeding at intervals for four months. As indicated in the tracing of the skiagram of the uterus before incising it and after the insertion of the capsules, the latter are in close proximity to the portion of the carcinoma replacing the uterine mucosa. Laboratory studies of the uterus indicated that these capsules were within 2 cm. of the most remote portion of the growth which had invaded the wall of the right uterine cornu. The entire mucosa of the entire uterine cavity would have been better covered with four or five capsules, the last two or three in tandem formation extending from the fundus well into the cervical canal (see next illustration).

We learned from these experiments many interesting and possibly important facts from the standpoint of the intimate application of radium to cancer actually or possibly present in the uterine mucosa.

In small uterine cavities of the triangular type, radium in capsules with tandem formation would be in close proximity to any carcinoma in the uterine mucosa. When a Y-shaped cavity was present the first
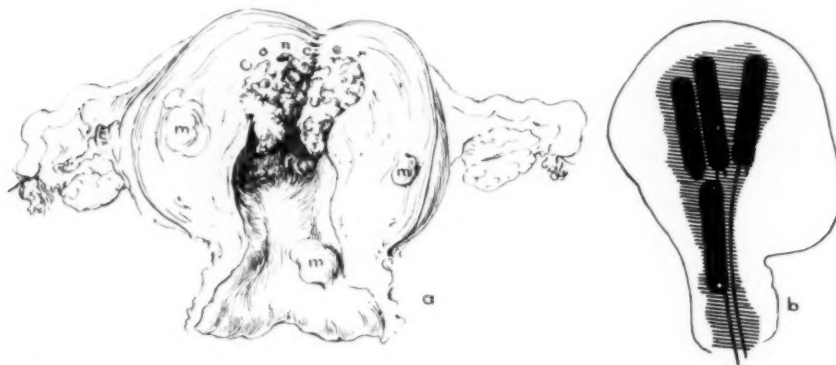
Fig. 10.—Carcinoma replacing the mucosa of the fundus, larger but much less invasive than the carcinoma in the preceding illustration ($\times \frac{1}{2}$). Patient (A. H. No. 8247-33), aged fifty-one years, bleeding of four years' duration. A "uterine polyp" had been removed in a hospital in another city three years before. The bleeding persisted. As indicated in the tracing of the skiagram of the uterus after the insertion of the capsules, the latter are in close proximity to the portion of the carcinoma replacing the uterine mucosa. In neither of the last two cases had the carcinoma extended into the uterine portions of the tubes.
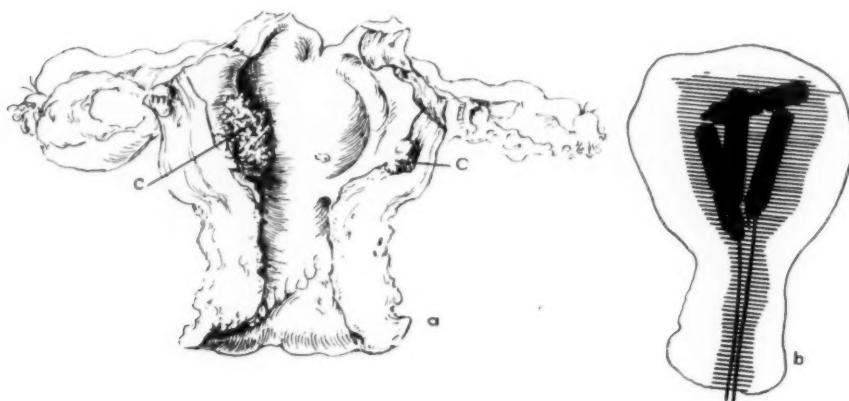
Fig. 11.—Carcinoma arising in the mucosa of the anterior uterine wall ($\times \frac{1}{2}$). Patient (A. H. No. 9185-33), aged sixty-one years, menopause at the age of fifty-two, bleeding of four months' duration. The carcinoma involves only a small area of the mucosa and grossly appears to be relatively benign. However, laboratory studies indicate that it is very invasive. As shown in the tracing of the skiagram of the uterus after the insertion of the capsules the latter are in close proximity to the portion of the growth presenting in the uterine cavity.

capsule would occupy one cornu, or strike the septum between the two cornua and go no further thus failing to reach either cornu. In some instances the first capsule on striking the septum between the cornua was turned back into the main uterine cavity. In medium-sized uterine

cavities the capsules in tandem formation did not cover the entire uterine mucosa as effectually as first placing a capsule in each cornu and then three or more capsules, tandem formation in a fountain pen
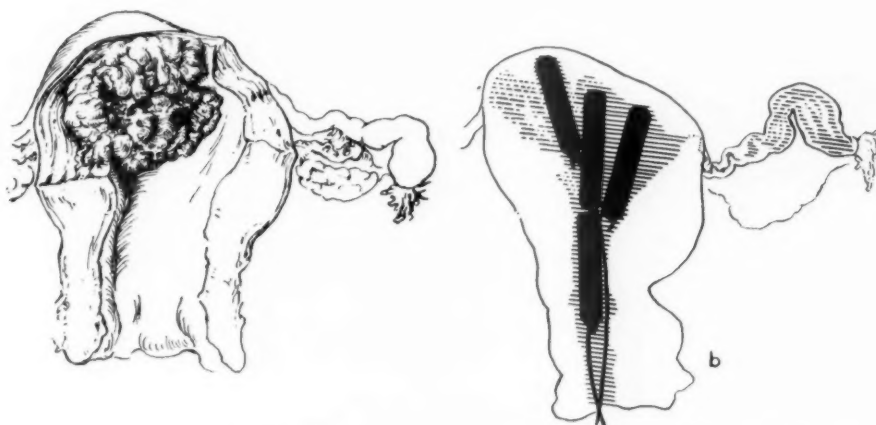
Fig. 12.—Carcinoma arising in the mucosa of the right uterine cornu with invasion of the uterine wall almost to its serosa ($\times\frac{1}{2}$). Patient (A. H. No. 1826-34), aged sixty-four years, menopause at the age of fifty-seven, bleeding of ten months' duration. As shown in the tracing of the skiagram of the uterus, the capsules are well placed so as to cover the portion of the growth presenting in the uterine cavity. Unfortunately their proximity to the actively growing and invading portions of the carcinoma is more remote. The sodium iodide solution has escaped into the lumen of the left tube and not that of the right. This frequently happened in these experiments when the uterine ostium of the tube was not obstructed by the growth.
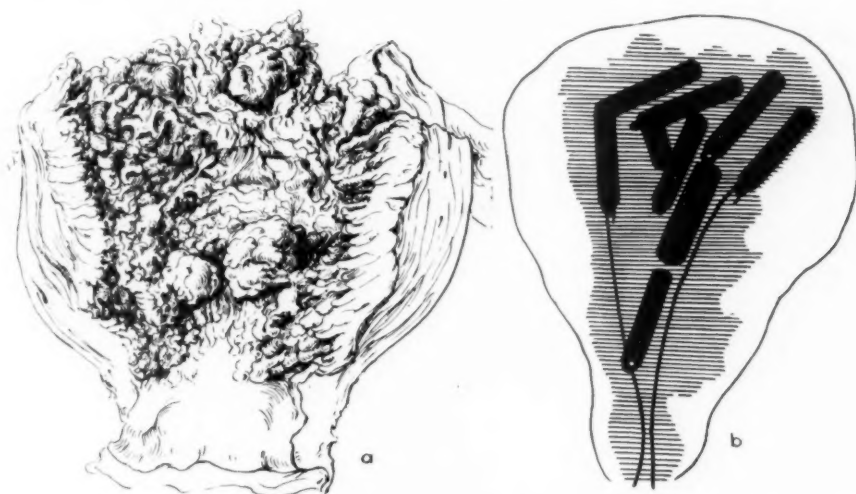
Fig. 13.—Carcinoma replacing the entire uterine mucosa with invasion of the uterine wall ($\times\frac{1}{2}$). Patient (A. H. No. 196-34), aged forty-nine years, menopause at the age of forty-four, bleeding of four and a half years' duration. The situation of the capsules introduced in the uterus is shown in the tracing of the skiagram of the uterus. The shaded area indicates the uterine cavity outlined by the sodium iodide solution. Even with many capsules we failed to place them in close proximity to all portions of the growth. A single tandem arrangement of three capsules would be much less effective.

rubber, so that they would extend from the fundus through the entire uterine cavity including the cervical canal. Large uterine cavities were

treated as above with the addition of more capsules. The capsules should be removed in the reverse order to that in which they were introduced. Even by these methods the capsules introduced in each cornu may fail to reach their destination, become displaced or capsules already in the uterine cavity may deflect those subsequently introduced. At best the adequate filling of the uterine cavity with the capsules is a matter of chance even in uterine cavities not distorted by submucous myomas, polyps, and carcinoma.

THE INFLUENCE OF MYOMAS AND LARGE POLYPI ON THE INTIMATE APPLICATION OF RADIUM TO ALL PORTIONS OF AN ASSOCIATED CARCINOMA OF THE BODY OF THE UTERUS

Myomas are frequently found in the uteri of patients with carcinoma of its body. The coincidence of the two conditions occurs so often that
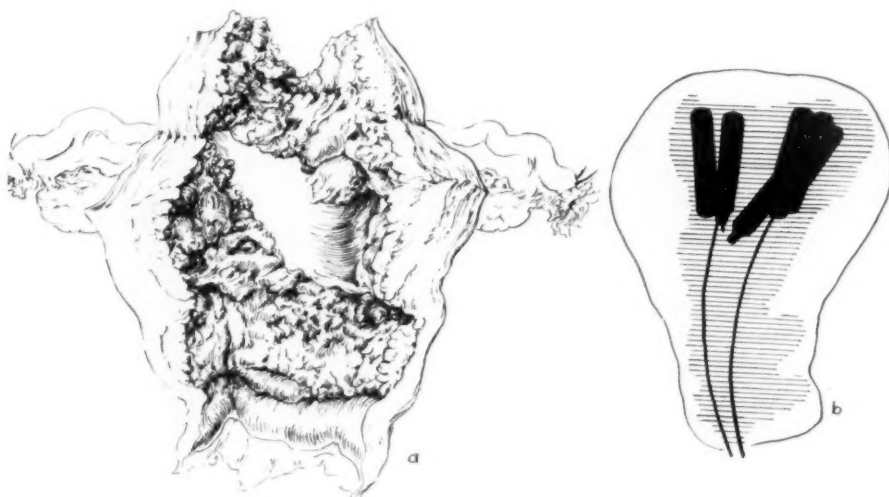
Fig. 14.—Carcinoma replacing the greater portion of the uterine mucosa with invasion of the uterine wall ($\times \frac{1}{2}$). Patient (A. H. No. 8783-33), aged fifty-two years, menopause at the age of fifty, irregular bleeding with a watery discharge ever since the menopause. The situation of the capsules introduced in the uterus after its removal is shown in the tracing of the skiagram. Due to faulty technic in placing the capsules they are in close proximity to only a small portion of the growth. Similar results might occur in the radium treatment of corpus carcinoma. In order to cover the mucosa of a uterine cavity of this size the capsules should extend from the fundus into the cervical canal, as well as being placed in each cornu.

many believe the myomas may, in some way, have a bearing on the etiology of the carcinoma later arising in the uterine mucosa. Some intramural myomas enlarge the uterine cavity (Figs. 15, 16, and 17). All submucous myomas distort the uterine cavity and may enlarge it. Endometrial polypi are also frequently associated with carcinoma of the body of the uterus. The carcinoma may arise in a benign polyp. These polyps distort the cavity and when large may distend it. An enlarged uterine cavity increases the uncertainty of intimately applying the radium to all parts of the growth (Figs. 18 and 19).

Submucous myomas and polyps may deflect the capsules of radium introduced through the cervix so that they may not reach all parts of the uterine cavity (Figs. 20 and 21). A portion or all of the carcinoma may be situated at one side of the myoma (Fig. 22) or large polyp.
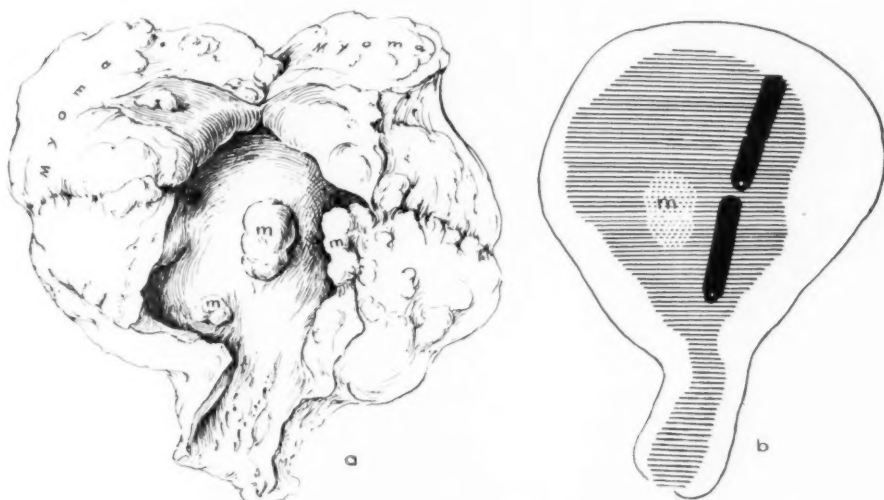
Fig. 15.—The influence of myomas on the intimate application of radium to all portions of the uterine mucosa. Uterus with multiple intramural and three small submucous myomas ($\times \frac{1}{2}$). Intramural and submucous myomas may enlarge the uterine cavity. Submucous myomas may intercept or deflect the capsules of radium so that they may not reach all portions of the uterine mucosa. If the submucous myomas are large, they may shield from the radium some or all of an associated carcinoma. The tracing of a skiagram of the same uterus, in which the cavity was filled with a solution of sodium iodide and two capsules, tandem formation, were introduced before incising the uterus, demonstrates that the capsules might not be in close proximity to an associated carcinoma which may arise in any portion of the mucosa. Myomas are frequently associated with corpus carcinomas.
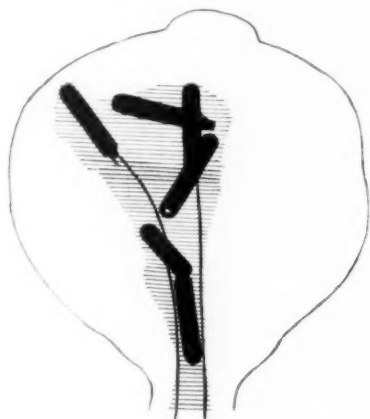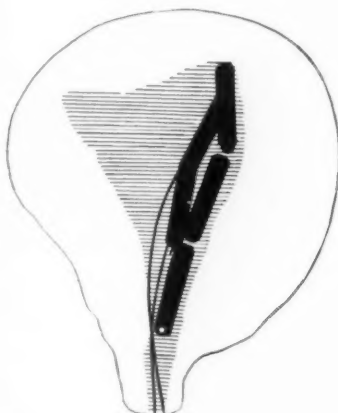
Fig. 16.   Fig. 17.

Figs. 16 and 17.—Tracings of skiagrams of two uteri with intramural myomas in which the enlarged uterine cavities have been filled with a sodium iodide solution and capsules have been introduced with an attempt first to place one in each cornu and others in tandem formation from the fundus well into the cervical canal. It is evident that this plan covers the mucosa of the entire cavity of these uteri better than a single tandem formation. Compare with Fig. 15. However, as indicated in Fig. 17, the capsules may fail to reach their destination or become displaced, even when they are introduced after the removal of the uterus.
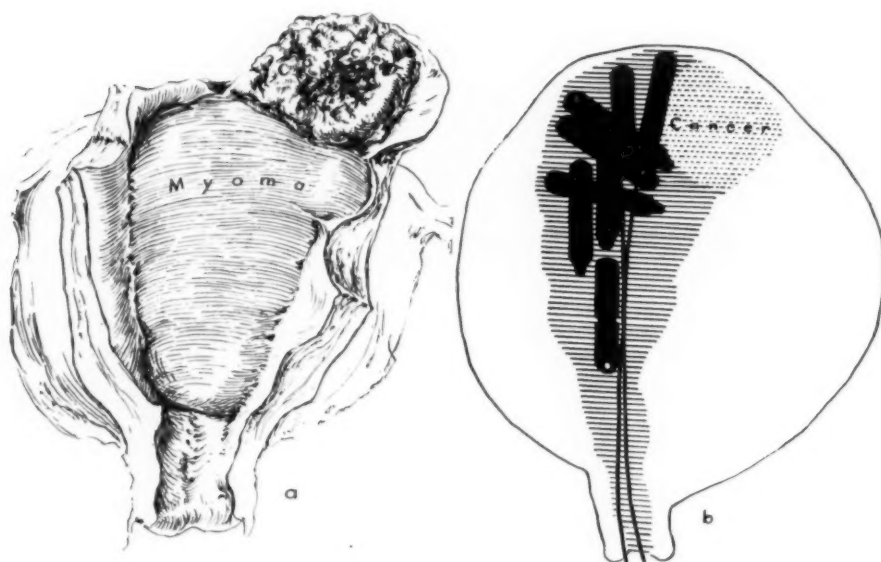
Fig. 18.—Carcinoma of the mucosa of the posterior wall of the right uterine cornu with deep invasion of the myometrium, associated with a large intramural myoma of the anterior wall of the uterus ($\times \frac{1}{2}$). Patient (A. H. No. 1027-34), aged seventy-three years, menopause at the age of fifty, bleeding of only one month's duration. The enlargement of the uterine cavity by the myoma and the situation of the carcinoma is shown in the first illustration. The capsules, introduced in the uterus after its removal, have reached all portions of the uterine cavity except that occupied by the carcinoma as indicated in the tracing of the skiagram of the uterus. Unfortunately the carcinoma has invaded the uterine wall so that this advancing portion is further away from the capsules than the growth presenting in the uterine cavity.
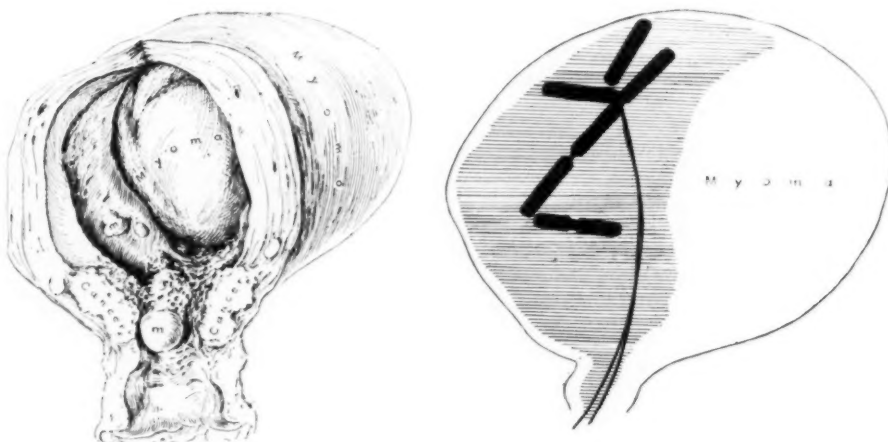
Fig. 19.—Carcinoma arising in the mucosa of the isthmus of the uterus with deep invasion of the uterine wall, associated with a large submucous myoma of the posterior uterine wall ($\times \frac{1}{2}$). Patient (A. H. No. 7540-33), aged sixty-three years, "menstruation" regular and normal until three months before her admission to the Albany Hospital. Since then the flow had been constant. An attempt was made to place a capsule in each cornu of the uterus after its removal and four capsules from the cervix to the fundus. The tracing of the skiagram indicates that the capsules are lost in the large uterine cavity and none of them are in close proximity to the carcinoma.

Should the capsules be placed only on the other side of the benign tumor the latter may shield the carcinoma from the radium.
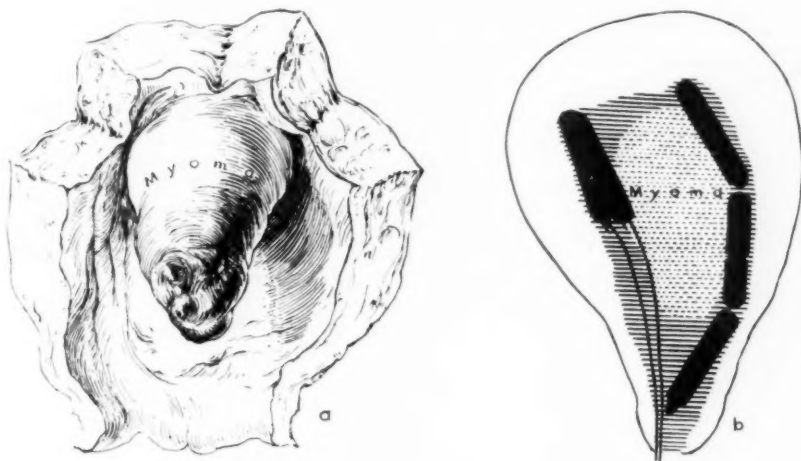
Fig. 20.—The influence of a submucous myoma on the intimate application of radium to all portions of the uterine mucosa ($\times \frac{1}{2}$). An attempt was made to place a capsule in each cornu of the uterus and three capsules tandem formation between these before incising the uterus. The tracing of the skiagram of the uterus indicates that this attempt was only partially successful. Since carcinoma may arise in any portion of the uterine mucosa, the chance of applying radium intimately to all or any of the growth is greatly lessened when a submucous myoma is present.
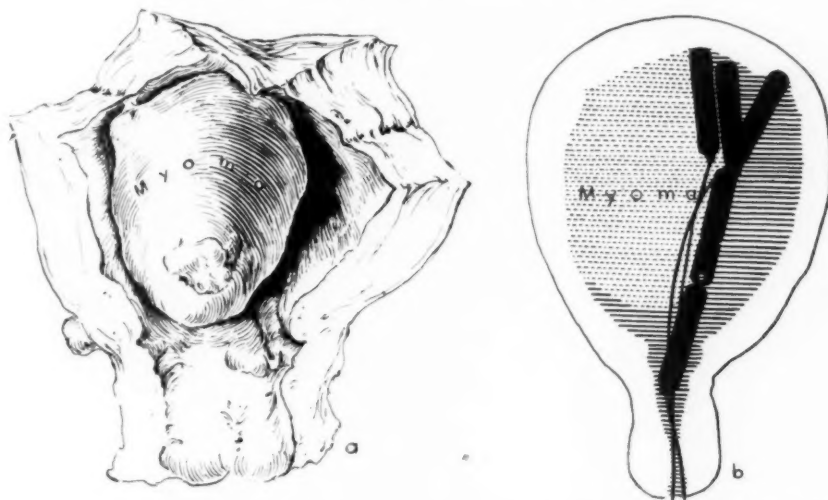
Fig. 21.—The influence of another submucous myoma on the intimate application of radium to all portions of the uterine mucosa ($\times \frac{1}{2}$). As indicated in the tracing of the skiagram of the uterus, the capsules introduced through the cervical canal were deflected by the myoma. Carcinoma arising in the uterine mucosa on the other side of the myoma would be shielded from the radium by the myoma. See Fig. 22.

LARGE CARCINOMAS FILLING AND DISTENDING THE UTERINE CAVITY

In some instances the uterus is enlarged by a carcinoma which has replaced all or a greater portion of its mucosa with or without a varying

degree of invasion of the uterine wall. In others the growth has arisen from a limited area of the mucosa and distends the uterine cavity like a submucous myoma. The carcinoma protruding into the cavity may deflect the capsules of radium just as submucous myoma and large polyps deflect them. Therefore the invading portion of the carcinoma is likely to be farthest away from the radium. This incomplete radiation, in a measure, can be corrected by having the patient return in from six to ten weeks for a check-up. A curettage may or may not disclose carcinoma. Radium may be used again. During the interim of six or ten weeks the actively growing carcinoma in the base of the tumor or in the uterine wall has had an opportunity to spread by continuous extension or metastasis. Also repeated curettages and radium applications are associated with increased trauma and the danger of disseminating the
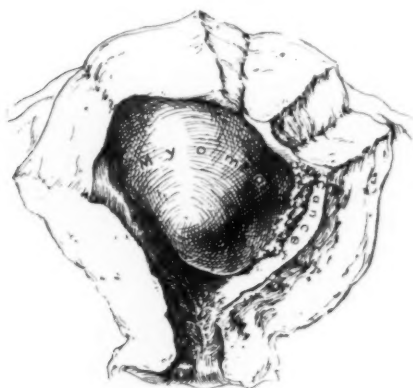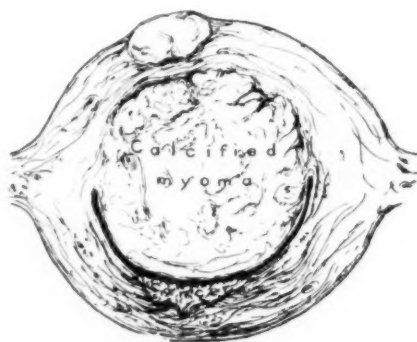
Fig. 22.   Fig. 23.

Fig. 22.—Superficial carcinoma of the uterus associated with a submucous myoma (×½). Patient (A. H. No. 73480), aged fifty-seven years, menopause at the age of fifty-two, bleeding of two years' duration. Hysterectomy Apr. 8, 1920. Patient at present is living and well over fourteen years since her operation. Had the patient been treated with intrauterine radium the capsules might easily have occupied the portion of the uterine cavity farthest away from the carcinoma which would have been shielded from the radium by the myoma.

Fig. 23.—Small invasive carcinoma arising in the mucosa of the anterior wall of the uterus, opposite a calcified submucous myoma. Cross-section of the uterus through the myoma and carcinoma (×½). The patient (A. H. No. 5217-32), aged seventy-five years, menopause at the age of fifty, had a diagnostic curettage, by me, Dec. 13, 1929, for slight inconstant spotting of two months' duration. Carcinoma was not found. The bleeding was judged to have arisen from either senile changes in the vaginal mucosa or from myomas which were readily detected on bimanual examination. Due to the negative findings, the age of the patient and her obesity operation was not advised. The bleeding ceased but reappeared in May, 1932. Another curettage was done June 11, 1932. A hematometra was found, but the carcinoma was not detected. The ovaries, tubes, and uterus were removed July 21, 1932. The patient made a satisfactory convalescence and felt well for over a year. At present she has a large pelvic tumor, evidently a recurrence. A mistake was made in not operating or employing radium at the time of her first admission to the hospital. Because of the submucous myoma, the chance of the intimate application of the capsules of radium to the carcinoma would have been greatly lessened.

carcinoma. A large uterus in a patient with carcinoma of the corpus uteri may be due to a large growth, associated myomas or hematometra. All of these may hamper the effective application of radium.

THE INFLUENCE OF THE DEPTH OF THE INVASION OF THE UTERINE WALL ON THE EFFECTIVE APPLICATION OF RADIUM TO THE INVADING PORTION OF THE CARCINOMA

The study of uteri, with carcinoma of the corpora, shows that the uterine wall is frequently invaded by the growth. The depth of this invasion varies greatly. Even when the carcinoma is confined to the uterus, some of it may be so situated as to escape the killing effects of radium in the uterine cavity. The effectiveness of the radium varies with the sensitivity of the growth and the distance between the remotest invading portion of the latter and the radium. This distance might be relatively great due to several factors such as: faulty technic in placing the capsules in the uterine cavity, a large growth filling the cavity, a bicornuate uterus with cancer in one or both cornua, submucous myomas,
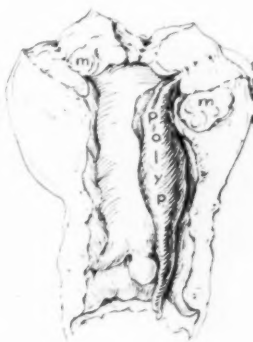
Fig. 24.   Fig. 25.

Figs. 24 and 25.—The influence of uterine polyps on the intimate application of radium to an associated carcinoma of the uterine mucosa. Benign polyps are frequently associated with corpus carcinomas and, like submucous myomas, may deflect the capsules of radium introduced through the cervix and may shield some or all of the carcinoma from the radium. Of great scientific interest and clinical importance is the development of carcinoma in a benign polyp. In Fig. 24 (A. H. No. 9108-33) is shown a uterus with two large polyps ($\times \frac{1}{2}$). One is histologically benign. In the other polyp carcinoma is present with involvement of the uterine mucosa about the base of the pedicle of the polyp. In Fig. 25 (A. H. No. 324-34), carcinoma is present in the base of a benign polyp and in the uterine mucosa about its pedicle with invasion of the uterine wall. All portions of benign polyps removed by curettage should be examined microscopically, and, if the uterus is not subsequently removed, the patient should be closely followed. Three instances of carcinoma arising in a benign endometrial polyp were encountered in the last seventeen cases of corpus carcinoma operated upon in the Gynecological Service of the Albany Hospital.

and polyps, and the depth of the invasion of the uterine wall, especially when it is in one or both cornua.

By continuous extension the carcinoma may pass through the entire uterine wall and penetrate its serosa. Occasionally peritoneal carcinomatosis arises in this manner, but more often nearby pelvic organs and structures become adherent to the peritoneal surface of the uterus thus penetrated and are invaded by the growth.

In five patients operated upon by the writer, the extension of the growth through the uterine wall had invaded portions of the intestinal tract. In two of these uterointestinal fistulas had developed. In all five patients the ovaries, tubes, and entire uterus were removed and the portions of the intestines invaded by the carcinoma were resected, in four of the five cases without severing the attachment of the intestine to the uterus. In three cases both a loop of the ileum and the sigmoid were invaded by the cancer and both were resected. One of the patients (A.H. No. 72119), aged forty years, died from peritonitis following the operation. Another patient (A.H. No. 4167-33), aged sixty-nine years, recovered from the operation but later died from metastases to the liver, spleen, kidneys, and lungs which were not detected at operation but dis-
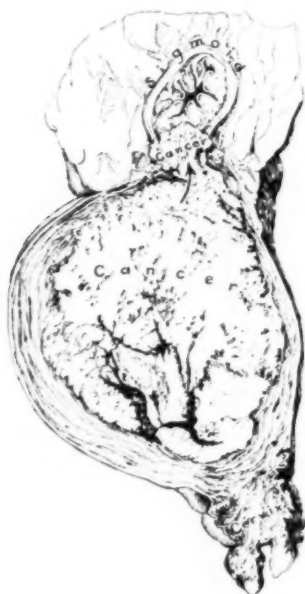
Fig. 26.—Extensive carcinoma of the body of the uterus with invasion of the sigmoid. Sagittal section of the uterus lateral to the cervical canal ($\times \frac{1}{2}$). Patient (A. H. No. 815-31), aged fifty-two years, menopause at the age of fifty, intermittent bleeding of six months' duration. By continuous extension the carcinoma has penetrated the uterine wall and invaded the sigmoid which is fused with the fundus of the uterus. The portion of the sigmoid adherent to the uterus was resected. An end-to-end anastomosis was done. The patient had an uneventful convalescence and is possibly cured three and a half years since the operation. It would be impossible, in this instance, to introduce capsules of radium through the cervix so that they would be in close proximity to all of the growth. It is also impossible to make an accurate pretreatment diagnosis of the extent of the growth in a patient with carcinoma of the body of the uterus.

covered at autopsy. Had metastases been detected at operation, the abdomen would have been closed without attempting to remove the uterus, and intrauterine radium would have been used. A third (A.H. No. 109500), aged fifty-two years (also with a double resection) was greatly benefited by the operation for over a year but died about eighteen months after the operation. The fourth patient (A.H. No. 815-31), aged fifty-two years, with resection of a portion of the sigmoid

is living and clinically free from cancer over three years since the operation (Fig. 26). In the fifth patient (A.H. No. 4780-33), aged fifty-six years, with resection of a portion of the ileum, only a year has elapsed since the operation. Only three of the five patients were greatly benefited by the operation, and only one is possibly cured. It may be claimed that radiotherapy would have given as good or even better results without any mortality and less morbidity.

The extension of the growth into the uterine wall as well as the exact situation and depth of this can be determined only by operation and the microscopic examination of the uterus removed. It would seem that in many of these cases radiation would not be as effective as the operative removal of the ovaries, tubes, and uterus. On the other hand Burnam[12] is quite confident from clinical observations that it is possible to cure by intrauterine radiation alone a very extensive uterine body cancer where the disease has not only involved the mucosa but extends all the way through the body of the uterus.

THE CONTINUOUS EXTENSION OF CARCINOMA OF THE BODY OF THE UTERUS THROUGH THE UTERINE OSTIUM OF THE TUBE INTO THE UTERINE PORTION OF THE LATTER

In several specimens of carcinoma of the body of the uterus in which the growth occupied one or both cornua, the distal portion of each cornu including the uterine portion of the tube and a part of its isthmus was carefully studied by microscopic sections (some in series) to determine whether or not the uterine growth had extended through the uterine ostium of the tube into its uterine portion. In every instance the mucosa of the uterine ostium of the tube had been replaced by the carcinoma, and in the majority of the specimens the growth also had extended a varying distance into the uterine portion of the tube. Since it is often difficult to determine the transition between the ostium and the uterine portion of the tube, especially when they are distorted by carcinoma, the exact extent of the invasion of the latter cannot be measured. I have encountered only one instance of the continuous extension of the growth through the entire uterine portion of the tube into its isthmus.

It is obvious that carcinoma in the uterine portion of the tube would not be as effectually acted upon by radium as that in the uterine cavity (Fig. 27). The distance between the radium in the uterine cavity and the growth in the uterine portion of the tube would be increased by several factors such as; faulty technic in placing the capsules, the size of the growth in the uterine cornu, a bicornuate uterus, submucous myomas, and the depth of the extension of the growth into the uterine portion of the tube.

CANCER EMBOLI MIGRATING ABOUT IN THE LUMINA OF THE TUBES

These emboli are usually few in number and very small. On the other hand, the lumen of the tube is relatively enormous. It is therefore a tedious task to exclude them. I have attempted this by embedding the entire tube and cutting the sections lengthwise in series. I much prefer the less scientific method of first fixing the tube, then cutting it into segments and examining many cross-sections from each segment. I am convinced that cancer emboli sometimes gain access to the lumina of the tubes prior to the trauma of bimanual examinations, curettage, radium application, and hysterectomy. The study of uterine cornua in which the growth has extended through the uterine ostium of the tube demonstrates that particles of cancer sometimes escape from the advancing growth in this situation into the lumen of the tube (see Figs. 30 to 35
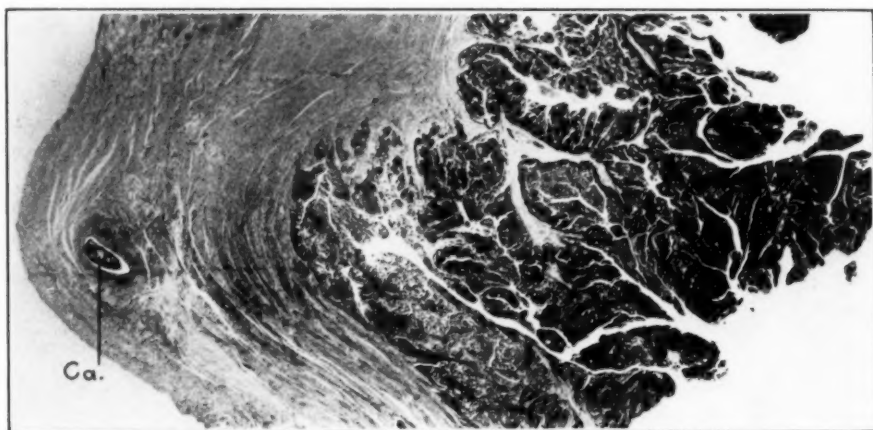
Fig. 27.—Photomicrograph (×3) of a horizontal section through the left uterine cornu including the uterine portion of the tube from a patient (A. H. No. 4856-32), aged fifty-four years, who had been bleeding almost constantly for twenty years. Carcinoma has replaced the entire uterine mucosa and in places has deeply invaded the uterine wall. By continuous extension it has passed through the uterine ostium of the left tube and penetrated the lumen of its uterine portion like a polyp. A cross-section of this extension into the lumen of the tube (ca.) appears in the photomicrograph. Because of the massive growth in this cornu it would be impossible to introduce a capsule of radium through the cervix so that it would be in close proximity to the carcinoma in the uterine portion of the tube. Carcinoma is frequently found in one or both cornua and often with extension into the uterine portion of the tube. Hence the importance of attempting to place a capsule of radium in each cornu.

inclusive of previous paper[13]), just as similar particles escape into the lumina of vessels and into the peritoneal cavity from carcinoma which has penetrated these structures. From my studies of cancer emboli in the tubes secondary to carcinoma of the body of the uterus and also of the ovaries, I am convinced that cancer cells in this situation may not only live for some time but may also increase in number just as I believe that they may live and multiply when floating about in the lumina of lymph vessels and in the peritoneal cavity. Trauma might

increase the casting off of these particles from the growth protruding into the lumina of the tubes and might further their migration toward or into the peritoneal cavity. The trauma incident to diagnostic procedures and the application of radium might force blood in the uterine cavity containing particles of cancer out through patent tubal ostia not occupied by carcinoma.

Would radium in the uterine cavity and deep x-rays destroy cancer cells in the tubes which were there prior to the introduction of the radium or resulted from it? Hysterectomy with the preliminary ligation of the distal ends of the tubes both prevents the further migration of these emboli and also removes all of them if they are confined to the lumina of the tubes.
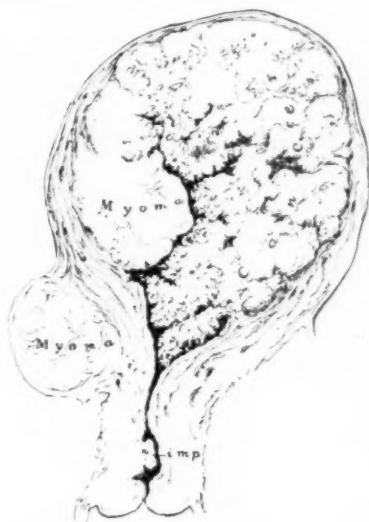
Fig. 28.—Sagittal section of a uterus ($\times \frac{1}{2}$) from a patient (A. H. No. 89234), aged sixty-two years, who had more or less constant bleeding of twelve years' duration. She had been curetted in a hospital in another city a year before I saw her. A diagnosis of carcinoma was made at that time, and the condition was considered inoperable. Since then she had had repeated x-ray treatments. An extensive carcinoma has distended the uterine cavity and in places has invaded its walls almost to the serosa. Multiple myomas are also present. In addition, metastases were present in the distal end of the left tube, the cervical mucosa and the vaginal wall (see Figs. 38 to 42 of previous paper[13]). The patient is living and clinically free from cancer over eleven years after the operation. It would be impossible, in this instance, to introduce capsules of radium into the uterine cavity through the cervix so that they would be in close proximity to all of the uterine growth. The carcinoma in the distal end of the left tube would be still farther away.

CARCINOMA OF THE TUBES ASSOCIATED WITH CARCINOMA OF THE BODY OF THE UTERUS

I have never seen an instance of carcinoma in both organs in which I judged that the growth was primary in the tube or the tumors in the two situations were of multicentric origin, but I realize that both of these phenomena may occur. Carcinoma of the uterine portion of the tubes from the continuous extension of the uterine tumor through the

uterine ostium of the tube is of frequent occurrence, and its significance on the effective application of radium has been discussed.

Fig. 29.—Posterior view of the uterus, tubes and ovaries ($\times\frac{1}{2}$) from a patient (A. H. No. 890-29), aged fifty-three years, who had bleeding of seven months' duration. The uterus is enlarged by multiple intramural myomas. A superficial papillary carcinoma has replaced the mucosa of the right uterine cornu. Multiple carcinomas, of different sizes and of the same histologic structure as that of the uterus, are present in the mucosa of the right tube (see Figs. 44 to 47 of previous paper[13]). The patient is living and clinically free from cancer over five years after the operation. Had a capsule of radium, by chance or intentionally, been placed in the right uterine cornu it would have been in close proximity to the carcinoma in that situation but not to that in the mucosa of the distal end of the right tube.
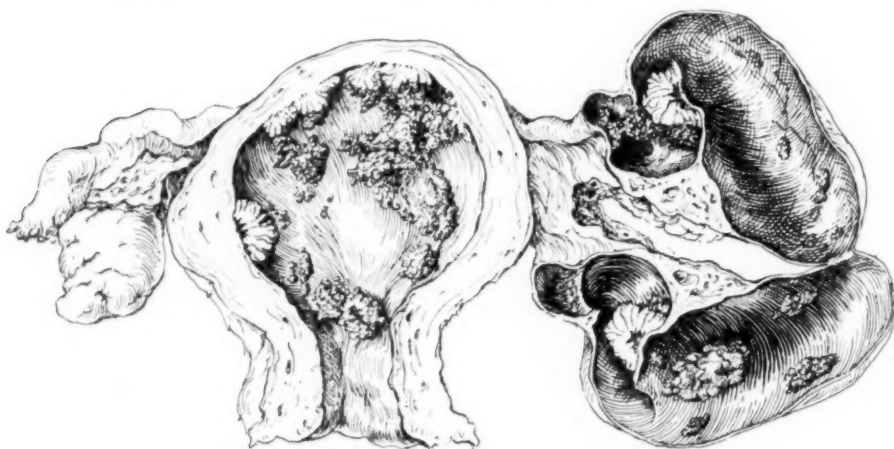
Fig. 30.—Uterus, tubes, and ovaries, the left tube incised longitudinally ($\times\frac{3}{5}$), from a patient (A. H. No. 3760-30), aged sixty-eight years, who had been bleeding for over a year. Multiple superficial papillary carcinomas of different sizes are present in the mucosa of the uterus and that of the left tube (see Figs. 60 to 67 of previous paper[13]). The patient is living and clinically free from cancer over four years after the operation. Multiple capsules of radium would cover the entire uterine mucosa but might be out of range of the carcinomas in the left tube. An exact diagnosis of the conditions present in these last three cases could be made only by the operative removal of the ovaries, tubes, and uterus and their laboratory study.

In a recent paper[13] by the writer on the pathogenesis of carcinoma of the tubes and of the ovaries secondary to that of the uterus, thirteen instances of these tumors occurring in 184 patients with carcinoma of the body of the uterus were reported.   Carcinoma in a tube and ovary was found in six cases, only in the tube or tubes (both tubes in one instance) in five and only in the ovary in two.   Only four of these patients were greatly benefited by the operation.   Three of the patients with secondary carcinoma of the tubes and not in the ovaries are still living and clinically free from carcinoma at intervals of eleven, five, and four years (Figs. 28, 29, and 30).   The intrauterine application of radium would probably not have given as good results as operation in these three cases.   The full extent of the carcinoma could not have been determined except by the laboratory study of the ovaries, tubes, and uterus.
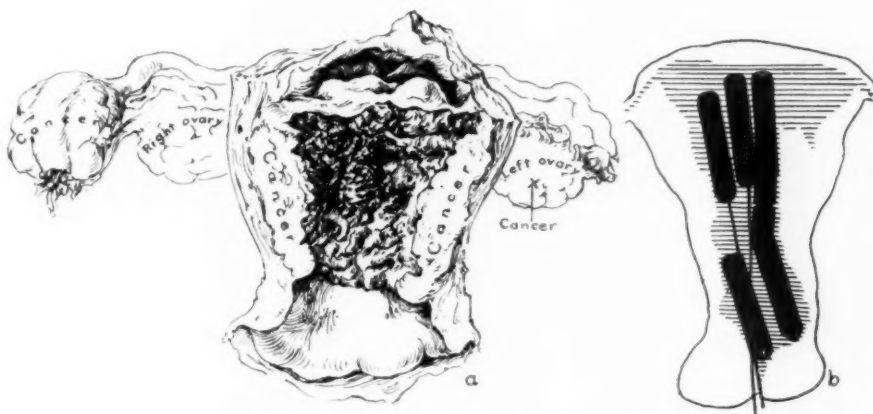
Fig. 31.—Infiltrating carcinoma probably arising in the mucosa of the isthmus and deeply invading the uterine wall: metastases in the mesosalpinx beneath the fimbriated end of the right tube and also in the left ovary ($\times \frac{1}{2}$). The patient (A. H. No. 136-34), aged fifty-eight years, menopause at the age of forty-nine, had a slight inconstant bloody discharge for nine months. The relation of the capsules, introduced into the uterine cavity before the uterus was incised, to the uterine growth is indicated in the tracing of the skiagram. The capsules are in close proximity to the primary tumor but not to the metastases. Radiation probably would not have destroyed the metastases. From my experience, in similar cases, I do not believe that the patient has been cured by operation.

CARCINOMA OF THE OVARY ASSOCIATED WITH CARCINOMA OF THE BODY OF THE UTERUS

These may be divided into three groups: (1) judged primary carcinoma of the uterus with secondary carcinoma in one or both ovaries; (2) judged primary carcinoma of the ovary with secondary carcinoma of the uterus; (3) carcinoma in both organs in which it is impossible to judge the site of the primary growth. Some of these may be of multicentric origin.

Group 1. I have studied eight cases in which the primary carcinoma was apparently in the uterus and the ovarian carcinomas, small and

seemingly of more recent origin, were judged to be secondary to the uterine tumor. In six of the eight cases carcinoma was also present in the tube accompanying the ovary. These eight cases have been fully reported in a previous paper.[13]

Operation was only of temporary value in the cases of this group which I have encountered. Intrauterine radium would probably have been just as effective as operation and that with a lower morbidity. Unfortunately the secondary carcinomas of the ovaries in this group could be detected only by their operative removal and laboratory study (Figs. 31, 32, and 33).

Group 2. I have never encountered a judged primary ovarian carcinoma associated with a very early carcinoma of the uterine mucosa. I have studied two cases, each with a carcinomatous ovarian cyst as-
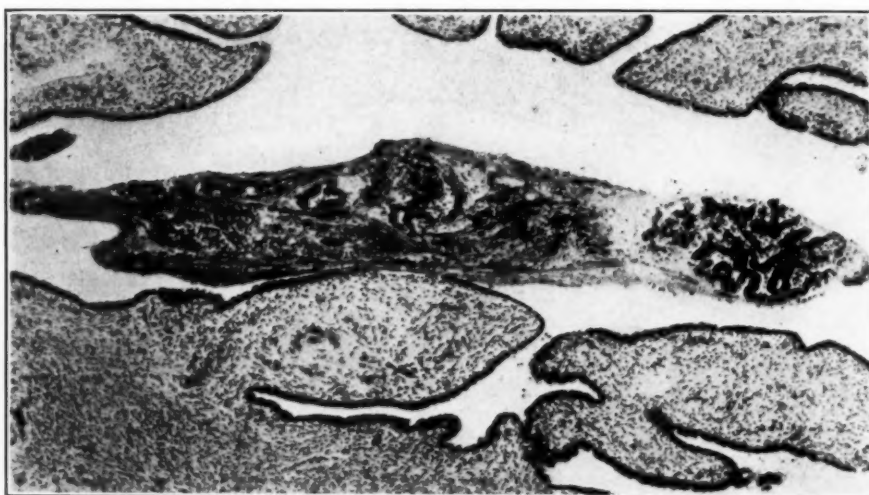
Fig. 32.—Photomicrograph (×54) of a portion of a longitudinal section of the left tube in Fig. 31 showing débris, with clumps of cancer cells, in its lumen. These were present in both tubes. The sodium iodide solution readily escaped from the uterine cavity into the lumina of both tubes and possibly carried with it the cancer cells shown in this illustration. Blood escaping from the uterine cavity into the lumina of the tubes will do the same whether occurring spontaneously or induced by bimanual examination, curettage, radium application, or hysterectomy. Both tubes were patent and pelvic adhesions were present. Pelvic peritoneal carcinomatosis was not noted but easily might have been overlooked. See Fig. 33.

sociated with a carcinoma of the uterine mucosa, in which I judged that the uterine growth was secondary to the ovarian. In one patient (A.H. No. 2031-31), aged fifty-two years, cancer was found only in the ovary and the uterus. The patient is still living and clinically free from cancer three years since the operation. In the other patient (A.H. No. 7211-30), aged sixty-one years, the right tube and ovary had been removed for an ovarian cyst in a hospital in another city three years before. Sections of the cyst were sent to Dr. James Ewing who made a diagnosis of adenocarcinoma. At her second operation, Oct. 11, 1930, the left tube and ovary and the

uterus were removed for an ovarian tumor. This ovarian cyst also was an adenocarcinoma of the same histologic structure as that of the opposite ovary removed at the previous operation. Adenocarcinoma of the uterus was present and was of the same histologic structure as the ovarian tumors. The patient is still living but has vaginal metastases which have been only partially controlled by radium. An examination of the tumor of the right ovary after its removal and before the closure of the abdominal incision at the first operation might have resulted in the removal of the opposite ovary, tube, and the uterus at that time even though they appeared normal.

Group 3. I have encountered four cases of carcinoma of the ovary and uterus in which I was unable to judge the site of the primary cancer. In one patient (A.H. No. 7052-28), aged sixty-one years, there was a carci-
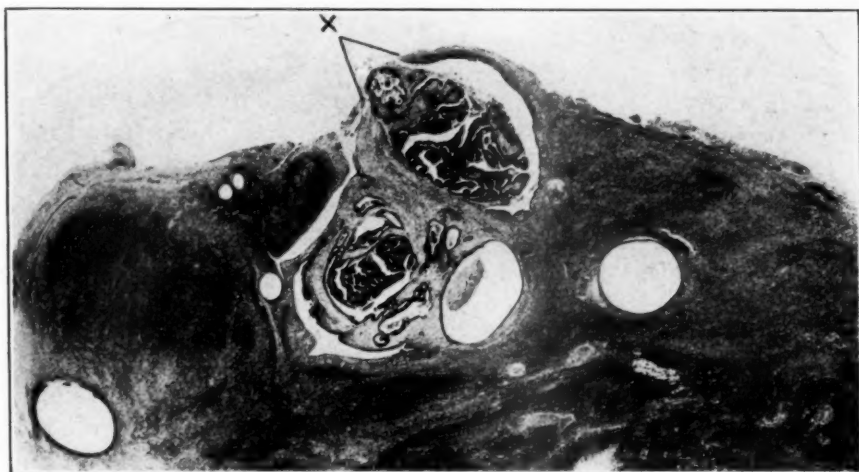
Fig. 33.—Photomicrograph (×10) of a portion of the left ovary in Fig. 31. Malignant endometriosis is present of the same histologic structure as the carcinoma of the uterine mucosa. It has developed in the wall of a cleft of the lateral surface of the ovary, a situation most favorable for the retention of foreign cells lodging on the surface of the ovary. It is of the encapsulated or foreign-body type with evidence (see X) that the encapsulation is not complete. It is a duplication, in its situation and general histologic structure, of many instances of benign ovarian endometrioses. There is strong circumstantial evidence that it might have arisen from the implantation of cancer cells escaping through the lumen of the tube. Cancer was not found elsewhere in the ovary. The metastasis of the right mesosalpinx of Fig. 31 is much larger, and therefore its pathogenesis is more difficult to judge. It also might be of implantation origin.

nomatous cyst of the right ovary and also an extensive carinoma in a large myomatous uterus; multiple carcinomas of different sizes were present in the mucosa of the tube. The histologic structure of the carcinomas in the three organs was the same and that of the uterus presented the histologic picture of having arisen in the endometrium. The opposite tube and ovary were normal. Peritoneal carcinomatosis was not present nor were any metastases detected at the operation. The ovaries, tubes, and entire uterus were removed. The patient survived the operation

but died four months later. At autopsy an extensive intraperitoneal hemorrhage was found, but its source was not determined. Metastases were found in the pelvic lymph nodes but not in any other tissue structure.

In the second patient (A.H. No. 94816), aged fifty-seven years, a carcinomatous cyst was present in the right ovary and an advanced infiltrating uterine carcinoma, which had invaded the entire wall of the uterus almost to its serosa. Carcinoma was not found in the tube. The ovaries, tubes, and entire uterus were removed Jan. 7, 1924. Vaginal metastases, which were present, were treated with radium. The patient made a satisfactory postoperative convalescence. She was last seen by me Nov. 20, 1933. She stated that she had been fairly well since the operation, nearly ten years ago, until the last year. Since then she had failed. A tumor was present in the upper right quadrant. Arrangements were made for the patient to be admitted to the Albany Hospital for observation, but she failed to come.

The third case of this group, a patient (A.H. No. 88548), aged sixty-three years, was fully reported in a previous paper.[14] Carcinoma of the same histologic structure was present in both ovaries and in the uterine mucosa. A very early peritoneal carcinomatosis was present. The patient survived the operation, was greatly improved, but later died from carcinoma. The intrauterine application of radium could not have destroyed the ovarian tumors. On the other hand, the removal of the ovaries, tubes and uterus gave her only temporary relief.

In the fourth patient (A.H. No. 5990-28), aged forty-six years, the right ovary was enlarged (size of an orange) and adherent. It presented the gross appearance of an endometrial cyst. Peritoneal endometriosis was present in the posterior culdesac. The ovaries, tubes, and uterus were removed Sept. 26, 1928. Adenocarcinoma of the same histologic structure was present in both the ovarian tumor and in the uterus. Carcinoma was not found in the tubes. The carcinoma in the right ovary was judged to have arisen in the epithelial lining of an endometrial cyst. The patient made a satisfactory convalescence and clinically is free from cancer nearly six years after the operation.

It is of clinical interest that none of the patients with small metastatic ovarian carcinomas from judged primary carcinoma of the body of the uterus were cured by operation. They probably would not have been cured by radiation. On the other hand, four of the six patients with carcinoma of the body of the uterus and a carcinomatous ovarian cyst, which was easily palpated on bimanual examination, were greatly benefited by operation. Two of them possibly may be cured. It is doubtful if radiation alone would have given as good results as operation in this last group.

It is important to bear in mind that enlarged adnexa in a patient with carcinoma of the body of the uterus may be due to carcinoma of the

ovaries or tubes. Also bleeding may be a manifestation of ovarian or tubal carcinoma when carcinoma is not found in the curettings from a suspected carcinoma of the body.

CARCINOMA OF THE BODY OF THE UTERUS WITH METASTASES TO OTHER STRUCTURES THAN THE TUBES AND OVARIES

Vaginal metastases are the only ones which lend themselves to the intimate application of radium. I am convinced, from my own experience, that radium is of great value in the treatment of these metastases. I have been able to obtain apparent clinical cures with radium both in cases in which they were present at the time of the hysterectomy and also when they have appeared afterward.

DANGERS ARISING FROM INTRAUTERINE RADIUM IN THE TREATMENT OF CARCINOMA OF THE BODY OF THE UTERUS

Aside from the limitations of radium in the treatment of this condition there are dangers associated with its use.

I would expect that extensive radium necrosis might frequently occur due to the amount of radium used, its length of time in the uterine cavity, the diminished blood supply of the senile uterus, and the frequent destruction of the uterine wall by the carcinoma. I have seen only one instance of extensive necrosis following the use of radium in carcinoma of the body of the uterus.

Often bacteria are present in necrotic carcinomas. The intrauterine application of radium may cause a spread of this infection. Instances of death from this source have been reported. I have seen a few instances in which the treatment of corpus carcinoma with intrauterine radium has been associated with a febrile reaction, but I have never observed any serious results. On the other hand, I have encountered one instance of fatal staphylococcus septicemia following the intrauterine application of radium in the treatment of cervical carcinoma.

As a result of the necrosis of a carcinoma which has invaded the uterine wall, the latter may be easily perforated during a diagnostic curettage. Such unfortunate accidents have been reported. I have encountered one to be reported later in this paper. It is quite possible in an unrecognized accident of this kind, that capsules of radium might be pushed through the perforation into the peritoneal cavity. Capsules also might be pushed through a portion of the uterine wall weakened by cancer invasion and necrosis without a previous perforation by the curette. I have never observed such an accident.

These are all real dangers to be considered and guarded against in the radium treatment of cancer in this situation. According to the literature, they are of infrequent occurrence.

Any trauma to an organ, the seat of carcinoma, may cause cancer cells to gain access to the lumina of veins and lymphatics or bring about a

further migration of cancer emboli already in these channels. A diagnostic curettage and the introduction of radium must, at times, be responsible for this form of dissemination.

The capsules of radium, when they are passed through the cervical canal into the uterine cavity, act like the piston of a syringe and may easily force any blood in the uterine cavity into or even through the lumina of patent tubes into the peritoneal cavity. Should bleeding occur in the uterine cavity, while the capsules are in place and drainage not be provided for through the cervical canal, blood containing cancer cells might escape through the lumina of patent tubes. I am convinced that the transtubal escape of blood from the uterine cavity during the intrauterine application of radium does occur and is responsible for the infection of the peritoneal cavity by both cancer cells and bacteria. I realize that metastases do not always follow such an accident nor does a fatal bacterial peritonitis necessarily result. It is possible that these potential metastases from cancer cells may be controlled by deep x-rays. I also realize that the dangers just mentioned do not outweigh the great value of intrauterine radium in hazardous operative risks.

Radium has been employed in the treatment of carcinoma of the body of the uterus in the Gynecological Service of the Albany Hospital, under the following conditions: (a) judged hazardous operative risks; (b) after hysterectomy in the treatment of cancer which had not been completely removed and vaginal metastases; and (c) where a mistake has been made in diagnosis or diagnosis was uncertain. Some of the immediate results have been most gratifying. The number of cases treated is small, and that with the short time that has elapsed since they were treated makes them of very little statistical value. I have operated on only four patients who have had a previous radium treatment. I shall report these four cases and one other.

<div align="center">CASE REPORTS</div>

CASE 1.—Extensive necrosis of the uterine wall following the intrauterine application of radium for ''diagnosed'' carcinoma of the body of the uterus. The patient (A. H. No. 7951-33), aged fifty-five years, complained of uterine bleeding of a year's duration. She had been married and had three children. The menopause occurred at the age of fifty. She had a curettage and an application of intrauterine radium in the form of 100 millicuries of radon for thirty hours at a hospital in another city on Sept. 4, 1933. This was followed by a febrile reaction of two weeks' duration. The curettings were examined microscopically and a diagnosis of adenocarcinoma made. I first saw her Oct. 10, 1933. There had not been any bleeding since the radium treatment. On bimanual examination the uterus was found to be enlarged and retroflexed but movable. I obtained the slide from which the original diagnosis of adenocarcinoma had been made. The section was so thick and poorly stained that I could not make a diagnosis. I also obtained some of the original curettings, but, because of poor fixation, unsatisfactory sections were obtained. I was unable to confirm the original diagnosis, and I hesitated to curette the uterus. On Nov. 2,

1933, the appendix, both tubes and ovaries, and the entire uterus were removed. A submucous myoma present in the fundus and an extensive necrosis of the posterior uterine wall which involved the entire wall to its serosa were found (Fig. 34). Cancer was not found in the specimen. The patient made a satisfactory postoperative convalescence.

CASE 2.—Remanifestation of carcinoma of the body of the uterus one year and four months after an apparent clinical cure, following the use of intrauterine radium. The patient (A. H. No. 4383-32), aged seventy-seven years, complained of uterine bleeding of two and one-half months' duration. She had been married and had one child. The menopause occurred at the age of fifty-eight. A diagnostic curettage was performed, and a papillary adenocarcinoma was found. The patient was obese and otherwise considered a hazardous operative risk. The uterus appeared to be small and freely movable. On June 24, 1932, 100 mg. of radium were introduced into the uterine cavity in two capsules, tandem formation (70-30) and left there for twenty-four hours. The patient was advised to return for a check-up in two months' time. She failed to appear until December, 1932. She felt well and had not had any bleed-
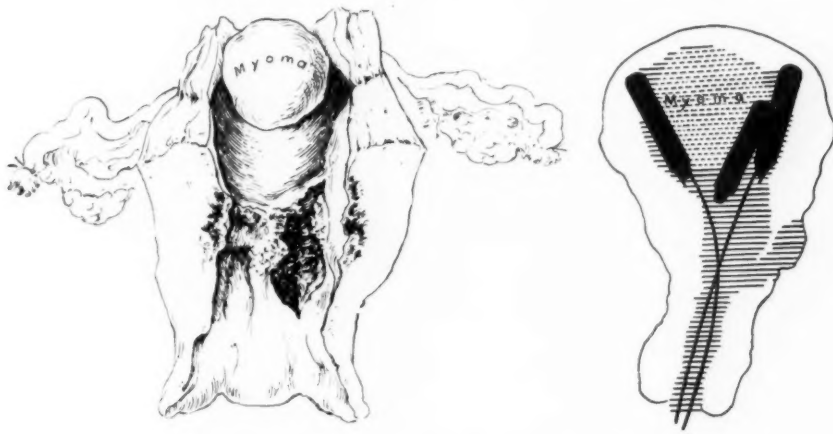
Fig. 34.—Extensive necrosis of the uterine wall (×½) following the intrauterine application of radium for diagnosed carcinoma of the body of the uterus fourteen weeks before (Case 1 of this paper). The necrosis, in places, involves the entire thickness of the uterine wall to its serosa. I believe that the capsule of radium probably struck the lower end of the submucous myoma and remained in the isthmus of the uterine cavity. The tracing of the skiagram of the uterus shows the uterine cavity enlarged by the necrosis and also the capsules which were introduced after removing the uterus and before incising it. A capsule is well placed in each cornu but the rest of the cavity would have been better covered by more capsules.

ing since the application of radium over five months before. A thorough curettage of the uterus was performed on Dec. 15, 1932. Carcinoma was not found. She was readmitted to the Albany Hospital Nov. 8, 1933. She felt well but had noticed a slight bloody discharge for only two weeks. The following day a biopsy was made, and carcinoma was found. One hundred milligrams of radium in four capsules were placed in the uterine cavity and left there for twenty-four hours. It may be said that the patient had not received the proper dosage of radium at the first treatment in June, 1932. On the other hand, the case well represents the false sense of security that may arise in the radium treatment of this disease.

CASE 3.—Adenocarcinoma of the body of the uterus, intrauterine application of radium, hysterectomy fourteen weeks later. Carcinoma was still present, lining the uterine cavity, especially that of both cornua and also in the lymphatics of the

uterine wall. The patient (A. H. No. 264-33), aged sixty-six years, complained of uterine bleeding of three years' duration. She was married and had two children, aged forty-seven and forty-five years. The menopause occurred at the age of fifty. On bimanual examination, Jan. 11, 1933, the cervical canal was found to be distended by a friable growth. The uterus appeared to be freely movable. My first impression was that an intracervical type of carcinoma was present. On Jan. 14, 1933, a more careful examination was made and tissue was obtained for microscopic diagnosis. As a result of this examination I was convinced that the cancer arose in the body of the uterus and had protruded through the cervical canal. Frozen sections showed an adenocarcinoma. The patient was short, obese and had lost a large amount of blood. Therefore, I decided to use radium. One hundred milligrams of radium in two capsules tandem formation (70-30) were introduced into the uterine cavity and left there for twenty-four hours. The patient was instructed to return in six weeks' time. At the end of that time she wrote to me stating that the bleeding had ceased and that she felt well, was unable to leave her home on account of sickness in the family, but would come back as soon as she could. I saw her in my office on April 25. She felt well and her general condition had improved greatly. Bleeding had occurred only on two occasions since the application of radium in January, the
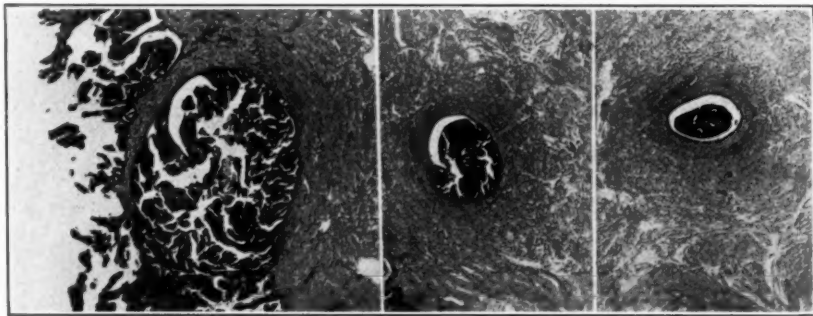
Fig. 35.—Three photomicrographs (×5) from a series of sections through the left uterine cornu of a uterus in which intrauterine radium had been employed four months before (Case 3 of this paper). The greater portion of the growth, distending the uterine cavity at the time of the application of the radium, was destroyed by the radium. Evidently the carcinoma in the uterine cornu and its extension into the lumen of the uterine portion of the tube were out of range of the radium in the uterine cavity which had been introduced in two capsules, tandem formation. A capsule in each cornu with two or three capsules, tandem formation, between these would have covered the growth much better in this instance.

last time three days before. On bimanual examination, the cervix appeared to be normal, and the uterus was freely movable.

On April 28 the ovaries, tubes, and entire uterus were removed. No evidence of metastases was detected at the operation. The tubes appeared to be patent. On incising the uterus after its removal, it was found that the greater position of the large growth, present at the time of the introduction of radium in January, had disappeared. On the other hand, carcinoma was still evident lining the entire uterine cavity and most abundant in both cornua (Fig. 35).

For the most part the growth was superficial with very little invasion of the uterine wall. Unfortunately in a few places carcinoma was found in judged lymph vessels in the deeper portions of the myometrium. The patient made a very satisfactory convalescence and when last heard from felt well. I believe that the prognosis would be better had radium not been used but the uterus removed when the patient was first seen fourteen weeks before.

CASE 4.—Carcinoma of the body of the uterus, intrauterine application of radium, followed by hysterectomy eleven days later. Blood and particles of cancer were found in the lumina of the tubes and blood in the pelvic cavity. The patient (A. H. No. 95802), aged fifty-three years, complained of uterine bleeding. She was married but had never been pregnant. Menstruation had been regular and normal until two years before when she flowed profusely for two weeks. Since then she had "menstruated irregularly." She had been flowing continuously for three months when I saw her. On pelvic examination the uterus was found to be slightly enlarged and freely movable. The patient was a large woman and had thick abdominal walls. A diagnostic curettage was advised. Feb. 27, 1924, the uterus was curetted and there was obtained a large amount of thickened endometrium, which grossly so closely resembled endometrial hyperplasia that radium was employed without waiting for a microscopic examination of the curettings. Fifty milligrams of radium were introduced in the uterine cavity and left there for twenty-four hours. The microscopic examination of the curettings showed adenocarcinoma which was reported after the patient had left the hospital. She returned to the hospital Mar. 9, 1924. At the
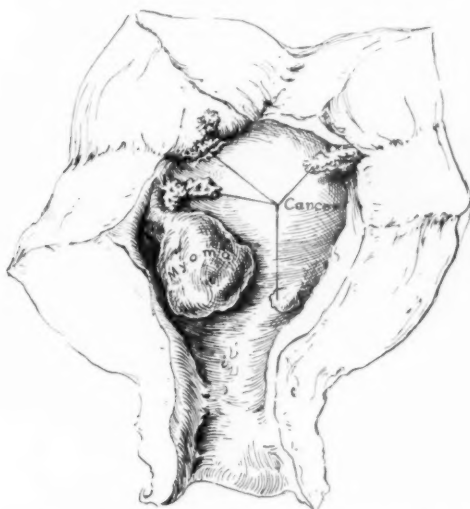
Fig. 36.—Uterus ($\times\frac{1}{2}$) removed eleven days after curettage and radium treatment (Case 4 of this paper). The uterus was thoroughly curetted after an erroneous diagnosis of hyperplasia of the uterine mucosa. As shown, patches of the growth and a submucous myoma were missed. Both tubes were distended with blood and a small amount of the latter was present in the posterior culdesac at the time of the operation.

operation the following morning, a small amount of bloody fluid was found in the posterior culdesac. Endometriosis was also present there. Both tubes were patent and distended with blood. The fimbriated ends of both tubes were ligated and the culdesac was wiped dry with gauze. The ovaries and tubes and entire uterus were removed. The patient made an uneventful recovery and has remained well.

On incising the uterus, after its removal, a small submucous myoma was present. The only carcinoma found in the uterus was in the form of small scattered patches superficially involving the endometrium (Figs. 36 and 37). The trauma of the curettage caused both bleeding and a dissemination of particles of cancer into the uterine cavity. The introduction of the capsule containing the radium through the cervical canal, like the piston of a syringe, undoubtedly forced some of the blood in the uterine cavity out through the patent tubes into the peritoneal cavity. Fortunately a peritoneal carcinomatosis did not arise. Had the introduction of

radium been deferred until after a microscopic examination of the curettings had been obtained, it would not have been used in this case. Hence the importance of a microscopic examination of curettings before using radium. Mistakes like this have led to the routine immediate or early diagnosis of all curettings in the Gynecological Service of the Albany Hospital.

CASE 5.—Carcinoma of the body of the uterus, intrauterine application of radium, hysterectomy two months later. Peritoneal carcinomatosis was present restricted to the pelvic structures and the omentum. Four months after the hysterectomy a metastasis was found in the scar of the abdominal incision. This case (A. H. No. 111-33) was fully reported in a previous paper.[13] The evidence indicating that the metastases to the ovaries, peritoneum of the pelvic structures, and omentum arose from the implantation of cancer cells escaping through the lumina of the patent tubes during the application of the radium is presented in Figs. 106 to 112, inclusive, of that paper. I believe that the patient might have been cured had radium not been used, but the ovaries, tubes, and uterus had been removed, by the technic described by me, when the patient was first admitted to the Albany Hospital.
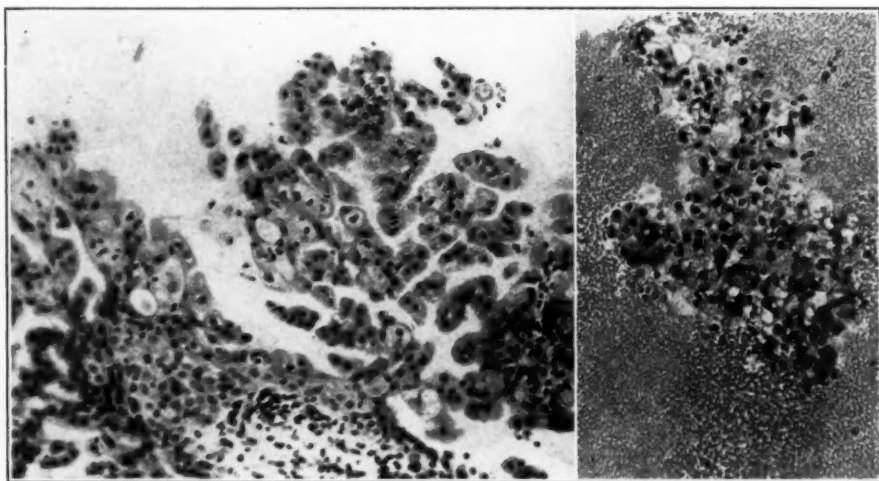
Fig. 37.—Two photomicrographs (×130): the first, of the curettings from the uterus shown in Fig. 36; the second, of the contents of one of the tubes removed with the uterus eleven days after the diagnostic curettage and radium treatment. Blood and a clump of cells of the same histologic structure as the primary uterine carcinoma are present in the lumen of the tube. The strongest possible circumstantial evidence indicates that the capsules of radium introduced through the cervix acted like the piston of a syringe and forced blood, containing cancer cells from the uterine cavity, into the lumina of the tubes. Cancer cells might thus escape into the peritoneal cavity and cause a peritoneal carcinomatosis even though the primary uterine tumor was destroyed by radium (see Case 5 of this paper).

The cases just reported represent the dangers and some of the unfortunate results of the radium treatment of carcinoma of the body of the uterus which I have observed. It may be said that radium is less to be criticized in these cases than mistakes in diagnosis, judgment, and the application of radium, as well as the failure to use deep x-rays.

TREATMENT OF CARCINOMA OF THE BODY OF THE UTERUS

The study of the ovaries, tubes, and uteri removed for corpus carcinoma convinces me that, in a large percentage of these cases, it is

possible with proper technic to place the radium in close proximity to all of the growth. Also these same studies demonstrate that frequently conditions are present which would prevent the ready escape of blood in the uterine cavity through the lumina of the tubes during the application of radium, such as tubes with very small lumina often present in women past the menopause, carcinoma occupying both uterine cornua, and the occlusion of the uterine portion of the tubes by previous inflammatory changes.

The removal of the ovaries, tubes, and uterus compared with the use of radium is difficult, the hospitalization long, the incapacitation and morbidity great, and the primary mortality high. On the other hand, the laboratory study of carcinoma of the body of the uterus shows that by operation all of the growth may be removed in cases where the intimate application of radium to it is a matter of chance or impossible.

Unfortunately conditions favorable or unfavorable for radium treatment can be definitely determined only by the removal of the ovaries, tubes, and uterus and their laboratory study. On the basis of laboratory studies alone operation should take precedence over radium in the treatment of this disease.

In my paper[14] published ten years ago, the danger of disseminating cancer cells in patients with carcinoma of the body of the uterus under the following conditions was discussed, namely: bimanual pelvic examination, diagnostic curettage, the intrauterine application of radium and hysterectomy. In the conclusions of that paper the following rules were stated for the diagnosis and treatment of patients in whom, from the clinical data, carcinoma of the body of the uterus is suspected:

1. A patient in whom cancer of the body of the uterus is suspected should be examined with great care and gentleness.

2. The diagnostic curettage should be employed only in doubtful cases or poor operative risks and, if used, should be done very gently.

3. Radium should not be used, as the capsule containing the radium acts as the plunger of a piston syringe, forcing the contents of the uterine cavity into the tubes.

4. Abdominal hysterectomy with the least possible manipulation of the uterus and with the closure of channels through which material may escape from the uterus into the field of operation offers the best chance for a permanent cure. The fimbriated ends of the fallopian tubes should be first ligated; the ovarian vessels, round ligaments, and uterine vessels should be doubly ligated, cutting between the ligatures; the vagina should be clamped below the cervix and carefully cleaned before severing the vagina below the clamp and removing the uterus.

During the last ten years we have tested those rules in the Gynecological Service of the Albany Hospital. We still believe in their fundamental principles. As a result of this experience and especially of our mistakes, we have both modified and amplified the methods of ten years ago.

Laboratory studies clearly indicate that bimanual pelvic examinations should be made gently. The vigorous massage of a uterus containing

carcinoma, incident to a difficult pelvic examination, may cause a dissemination of cancer cells into venous sinuses, lymphatics, and through the lumina of the tubes.

A positive diagnosis of carcinoma of the body of the uterus usually cannot be made except by hysterectomy or a diagnositic curettage. Occasionally the latter procedure will fail to obtain some of the growth as has been discussed. A diagnostic curettage may be termed a dangerous procedure even with experienced operators (Figs. 38 and 39). There is the danger of causing a dissemination of cancer cells into the venous sinuses and lymphatics. There is also the possibility of causing a dissemination of blood containing cancer cells into the lumina of the tubes and even through these channels into the peritoneal cavity. I have been able to demonstrate this unfortunate accident. I have never encountered the spread of bacterial infection as the result of the curettage of a uterus with carcinoma of its body. On the other hand, I have
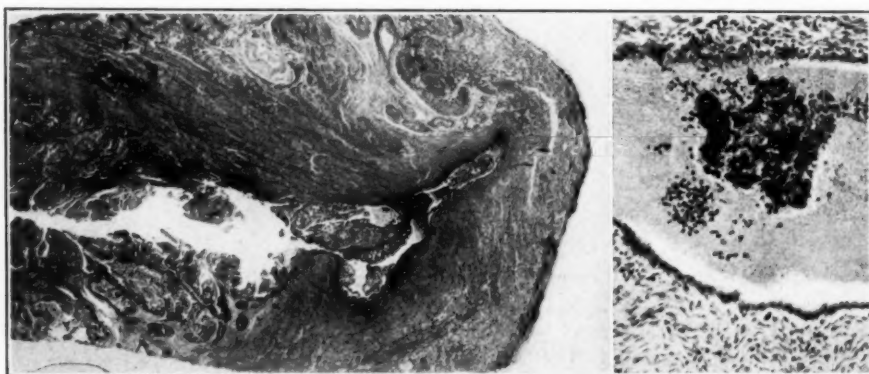
Fig. 38.—Two photomicrographs: the first ($\times 2\frac{1}{2}$) is of a portion of a longitudinal section through the right cornu of the uterus from which Fig. 27 was obtained, and the second ($\times 100$) is of a portion of a longitudinal section of the isthmus of the tube. The uterine ostium of the tube is patent. Blood escaping through the patent ostium might carry cancer cells with it into the lumen of the tube and even beyond into the peritoneal cavity. Blood and a clump of cancer cells are present in the lumen of the tube. This phenomenon might occur spontaneously or result from the trauma of bimanual examination, curettage, the application of radium, and hysterectomy. It is one of the dangers of these diagnostic and therapeutic procedures. The ligation of the fimbriated ends of the tubes at the onset of the operation, as advocated by the writer[14] ten years ago, prevents the escape of the contents of these tubes into the peritoneal cavity during the manipulations incident to hysterectomy. See Fig. 40.

been guilty of one instance of perforating the wall of a carcinomatous uterus associated with multiple myomas. The possibility of this accident was suspected at the time of the curettage but not definitely proved. The patient refused to have the major operation at that time but later consented. At the operation two months afterward an extensive carcinoma of the body was found as well as the suspected perforation. The latter occurred through the anterior wall of the uterus just above the vesicouterine reflection of peritoneum (the uterus was retroflexed). The carcinoma had grown through the perforation and had invaded a loop of the ileum. The sigmoid also was adherent to the fundus of the uterus

and was evidently invaded by the growth. Since carcinoma was not detected elsewhere, the ovaries, tubes and entire uterus were removed and the portions of the intestines invaded by the carcinoma were resected. The patient survived the operation but later died of metastases (A. H., No. 4167-33, previously mentioned in this paper).

As the result of laboratory studies of carcinoma of the uterus and likewise from clinical experience, I dread a diagnostic curettage in these cases. However, I realize its great value in the intelligent application of radium and that hysterectomy should not be done as a routine procedure in all patients in whom carcinoma of the body is suspected. It is our practice to make a biopsy in all of these patients who are poor operative risks. It is also made in good operative risks, but only when there are no other indications for an abdominal operation than uterine
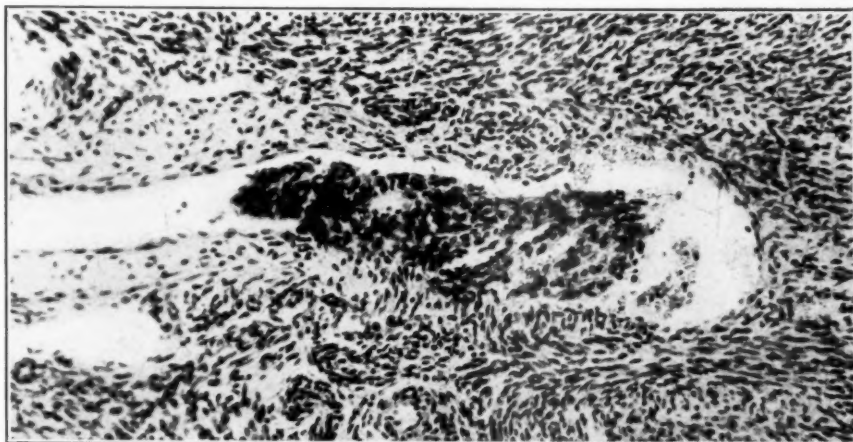
Fig. 39.—Photomicrograph (×130) of an endothelial-lined sinus or vessel of the uterine wall beneath the base of the actively invasive carcinoma of the body of the uterus shown in Fig. 10. Carcinoma and blood are present in this vessel. The carcinoma is not only fused with the wall but appears to be invading it. The connective tissue cells in the wall of the vessel beneath the carcinoma are more numerous than similar cells in other portions of this wall. Their course (polarity) is different. They appear to be headed toward the carcinoma above them. The block from which this section was cut included the primary growth and the entire thickness of the wall of the uterus and was made after the specimen had been hardened in formalin. For the above reasons I believe that this phenomenon was not created in blocking the tissue. Serial sections demonstrated that the carcinoma in this situation was not continuous with the primary tumor. It appears to be of recent origin. A diagnostic curettage was done in a hospital in another city sixteen days before the major operation. It was reported that great difficulty was encountered in obtaining sufficient tissue for diagnosis. This usually indicates much manipulation and great trauma, factors favorable for the dissemination of cancer. Hence the importance of gentle manipulations in the diagnosis and treatment of cancer of the body of the uterus, an early or immediate operation after biopsy, the use of deep x-ray therapy after radium treatment, and the preliminary closure of all avenues by which cancer cells may escape from the uterus in hysterectomy for this disease. See Fig. 40.

bleeding or a suspicious discharge. The contributory indications for an abdominal operation in women past the menopause who are good surgical risks are an enlarged uterus, enlarged adnexa, and pelvic discomfort from adhesions or conditions resulting from the injuries of childbirth.

Every patient with a history of abnormal uterine bleeding, no matter how slight or infrequent, should have an exact diagnosis. If this cannot be made from the history and clinical study of the case and if an abdominal operation for other reasons is not indicated, a biopsy should be made.

The material for the biopsy in suspected corpus carcinoma is obtained in the following manner: In the majority of parous women and even in some nulliparas, this is usually done with the patient in the Sims position and without an anesthetic. The direction and length of the uterine cavity is first ascertained by means of a uterine sound. This is followed by a minimum or no dilatation of the cervix. A small ovum forceps is gently inserted through the cervical canal into the uterine cavity. Sufficient tissue for microscopic examination is carefully removed. If this tissue in the gross suggests carcinoma, no further manipulation is done until after frozen sections are made and examined. If carcinoma is not found in the frozen sections, the uterine cavity is thoroughly explored with ovum forceps and curette. Should the further exploration of the uterine cavity be painful, nitrous oxide and oxygen anesthesia is used. If carcinoma is found in the frozen sections and the patient is a good surgical risk, the major operation is done as soon as possible. Patients in whom corpus carcinoma is suspected and hysterectomy is not clearly in-
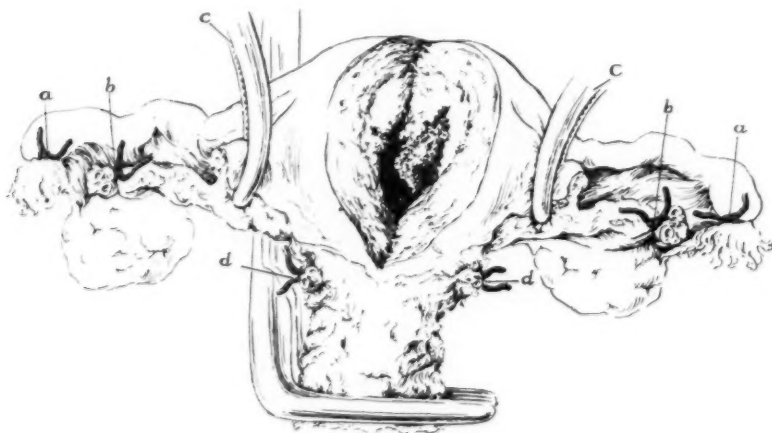
Fig. 40.—Methods employed to prevent the escape of cancer cells from the uterus during hysterectomy for corpus carcinoma (×½). This is the same illustration published by the writer[14] ten years ago, to which a clamp (c and c) has been added to each round ligament. By grasping these clamps the uterus may be removed with a minimal amount of trauma.

dicated without a biopsy usually come to the operating room prepared for the major operation. In every instance curettings are fixed in Zenker's solution, imbedded in paraffin, and excellent sections are obtained in twenty-four hours or sooner if urgent. This we believe is of great importance not only to obtain permanent sections but also better to enable us to make an early diagnosis when the amount of material obtained by curettage is small or the results of the microscopic examination of the frozen sections are uncertain.

The technic of the operation for carcinoma of the body of the uterus which we now employ is similar to that outlined in the previous article with the following change (Fig. 40): If the fimbriated ends of the tubes are patent and appear normal, they are ligated just back of the fimbriae.

If the fimbriae in any way suggest the presence of carcinoma in them, the tube and ovary are removed by severing their attachments to the uterus with a cautery. The reason for adopting this latter procedure is that carcinoma was found in the fimbriae of three patients in whom the tubes had been ligated back of the fimbriae.

We have learned that in all hysterectomies, in cases in which there is a history of uterine bleeding but carcinoma of the body of the uterus is not suspected and one or both ovaries are conserved, the uterus should be incised before the abdomen is closed. This applies especially to uteri with myomas. If carcinoma is found, the tubes and ovaries should be removed. In all operations in which a tube and ovary are removed for an ovarian tumor, the ovarian tumor should be incised, and if necessary frozen sections made and examined before closing the abdomen. If carcinoma is found, the remaining ovary, tube, and the uterus should be removed even though they appear to be normal.

I have operated upon only four patients who had previously been treated with intrauterine radium (see Cases 1, 3, 4, and 5 of this paper). The operation apparently was not made more difficult by the radium treatment. The general condition of two of the patients (Cases 3 and 5) had greatly improved after the radium treatment, thus making them better surgical risks. I fully realize that these cases are of little statistical value and that deep x-rays possibly may destroy cancer emboli disseminated by curettage and the application of radium. Therefore, it is hoped that the advantages of the preoperative treatment of carcinoma of the body of the uterus by intrauterine radium and deep x-rays as recommended by Healy may outweigh the dangers associated with the use of radium.

Laboratory studies indicate that many patients with carcinoma of the body of the uterus may be cured by intrauterine radium alone. Clinical experience has confirmed these indications. Therefore, radium is of great value in selected cases.

1. Most important of all is its use in hazardous surgical risks, especially in elderly obese women with a short expectancy of life.

2. If metastases are found in an abdominal operation for carcinoma of the body of the uterus and the removal of the ovaries, tubes, and uterus is difficult or evidently may not completely remove the entire local growth, it may be wise to close the abdominal incision and employ radium.

3. As an adjunct to hysterectomy—I have had a few cases in which I thought that the entire local growth had not been removed by operation. These were treated by placing capsules of radium in contact with the suspected areas at the time of operation and carefully shielding other structures with gauze. The capsules were removed later through the vagina or abdominal incision by means of the fish lines which had been attached to them.

4. Vaginal metastases present at the time of the operation or appearing afterward.

5. Definitely inoperable carcinomas.

6. The value of both the preoperative and postoperative treatment of these cases with radium and deep x-rays has been emphasized by Healy.

An attempt is being made to ascertain the results of the operative treatment of carcinoma of the body of the uterus in the Gynecological Service of the Albany Hospital from Jan. 1, 1909, to Jan. 1, 1934. We have encountered great difficulty in tracing patients operated upon several years ago, when they were not followed as closely as they have been in recent years. The desired data, at present, is incomplete. Fortunately it is being added to from time to time. Believing that carcinoma of the body of the uterus often grows slowly and that metastases may be absent even in advanced cases, we have made it our policy to operate on all patients with this disease, even seemingly poor surgical risks. This policy has increased our operative mortality and lowered our percentage of cures. In recent years we have been more conservative by employing radium in hazardous surgical risks and also in patients in whom the growth is obviously irremovable. During the period just mentioned, 204 patients were operated upon with 12 operative deaths, giving an operative mortality of nearly 6 per cent. From Jan. 1, 1909, to Jan. 1, 1929, there were 110 patients who survived the operation. We have traced 85 of these. Twenty-three died within five years. The cause of death in all of these cases could not be determined. Since our data are incomplete, we are planning to publish our results later.

SUMMARY AND CONCLUSIONS

The efficiency of intrauterine radium in a given carcinoma of the body of the uterus depends upon the following factors:

1. The sensitivity of the entire growth to radium. This varies in different cases and possibly also may vary in different portions of the same tumor since these portions may differ in their histologic structure.

2. The proper placing of the capsules in the uterine cavity and the correct dosage.

3. The proximity of the radium to all of the growth, especially the invading portions which are farthest away from the radium. Irrespective of the radiosensitivity of a given carcinoma of the body of the uterus, its curability by radium must in a large measure depend on the proximity of the entire growth to the radium in the uterine cavity. The closer this proximity, the greater the chance for a cure, especially in radioresistant tumors.

From the standpoint of the intimate application of radium to all of the growth, carcinoma of the body of the uterus may be divided into three groups.

Group 1. Those in which the intimate application of the radium to all of the carcinoma can be readily accomplished. Superficial growths restricted to the uterine mucosa or only slightly invading the uterine wall in small uteri with small cavities and thin walls normally present in women past the menopause.

Group 2. Those in which the intimate application of radium to all of the growth is possible, but conditions may render it a matter of chance. The laboratory study of uteri with corpus carcinoma suggests that this might frequently occur. Skiagrams of uteri removed at operation, with and without carcinoma of its body, in which capsules have been placed in their cavities as in the radium treatment of this disease show the relation of these capsules to carcinoma actually or supposedly present. These studies demonstrate that the intimate application of the radium to any or all of the growth may be a matter of chance under the following conditions:

A. Faulty technic in placing the capsules in the uterine cavity.

B. Large uterine cavities.

C. Cavities of the ''Y'' type with carcinoma in one or both cornua frequently with a continuous extension of the growth into the uterine portion of the tube.

D. Intramural myomas enlarging the uterine cavity. Submucous myomas which may deflect the capsules when they are introduced into the uterine cavity and may shield some or all of the growth from the radium. Because of the frequent association of uterine myomas with corpus carcinoma, this group is a very important one.

E. Large polyps which like submucous myomas may deflect the capsules and shield the growth from the radium.

F. Bulky carcinomas filling and distending the uterine cavity like submucous myomas.

Two or more of the above mentioned factors may occur in a given case.

These experiments demonstrate that two or more capsules, in tandem formation extending from the fundus through the uterine cavity well into the cervical canal, will cover all portions of a small uterine cavity except when it is of the ''Y'' or bicornuate type. Since it is impossible to ascertain the type of the uterine cavity prior to the introduction of the radium and also since the growth frequently occupies one or both cornua even with extension into the uterine portion of the tube, a capsule first placed in each cornu and then two or more capsules in tandem formation between these extending from the fundus well into the cervical canal will cover all portions of the uterine cavity more effectually than the single tandem formation, especially when the uterine cavity is enlarged. In very large uterine cavities the above arrangement may be supplemented by the introduction of additional capsules.

Group 3. Those in which it is impossible to apply intrauterine radium intimately to all of the growth.

A. The deep invasion of the uterine wall by the tumor and also its extension into adjacent structures. The distance between the radium and the invading portions of the growth may be increased by any of the factors described in the preceding group.

B. Cancer emboli in lymphatics, veins, and the lumina of the tubes.

C. Associated carcinoma of the tubes and ovaries and metastases to other structures than the vagina. Associated carcinoma of the tubes and ovaries form a small but important group. It would seem that carcinoma in these organs would be out of killing range of the radium in the uterine cavity. Some of these cases apparently have been cured by surgery.

Unfortunately the conditions just enumerated, which may make the intimate application of intrauterine radium to all of the growth favorable, a matter of chance, or impossible, can be determined with certainty only by the removal of the ovaries, tubes, and entire uterus and their laboratory study. Even then metastases to other structures are present in some instances.

More than one histologic type of carcinoma may be present in different portions of the same growth. A diagnostic curettage may obtain tissue from only one portion and therefore may not furnish accurate information of the true situation.

The failure to find carcinoma in a check-up curettage, from six to ten weeks or even in twice that time after radium treatment, does not prove that carcinoma is not present in areas not reached by the curette. This sometimes leads to a false sense of security and may be responsible for the death of the patient.

The intrauterine application of radium in the treatment of corpus carcinoma may cause the spread of bacterial infection; the wall of the uterus may be perforated by the capsules, and also extensive necrosis may result. According to the literature, these are of infrequent occurrence. Cancer cells may be disseminated into lymphatics, veins, and the lumina of the tubes. Ovarian and peritoneal carcinomatosis has resulted from the transtubal dissemination of these cells. It is hoped that the deep x-rays may destroy these potential metastases.

In spite of the uncertainties, limitations, and dangers of intrauterine radium in the treatment of carcinoma of the body of the uterus, it is of the greatest value in many instances.

We are much better able to judge the condition of the patient as a surgical risk than we can foretell if all of the growth can be reached by radium. Because of the inability to make an accurate pretreatment diagnosis of the exact situation and extent of the growth and the fact that all of the carcinoma may sometimes be removed where radium would

fail, the removal of the ovaries, tubes, and the entire uterus, with an attempt to prevent the dissemination of the carcinoma, is indicated in patients who are good surgical risks.

Laboratory studies suggest and clinical experience has demonstrated that intrauterine radium is effective in many cases. Therefore, it is indicated in hazardous surgical risks, especially when the uterus is small and the adnexa are not enlarged. It is also indicated in evident irremovable carcinomas.

The preoperative treatment of corpus carcinoma by intrauterine radium followed by deep x-ray therapy is logical if deep x-rays will destroy cancer cells disseminated by curettage and the application of radium. For like reasons postoperative radiation is indicated to destroy cancer emboli disseminated by the operation.

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Klaften: Granulosa Cell Tumors of the Ovary, Arch. f. Gynäk. 150: 643, 1932.

Klaften reports ten cases of granulosa cell tumors of the ovary encountered in the past four years. The histologic structure of these tumors resembles, but is not identical with the granulosa cells. Meyer believes that there is a functional similarity due to the hormonal effects produced by the tumor. Before puberty, these tumors produce uterine bleeding, breast hypertrophy and the development of the secondary sex characteristics. In sexually mature women, the breasts enlarge, become hyperactive and the entire uterus undergoes a very definite hypertrophy.

The author believes that this type of tumor is more common than it is considered to be at present. In his material the incidence was 4.4 per cent. These tumors occur at any age from early childhood to old age but are most frequent between thirty and sixty. Bilateral involvement occurred in 6 per cent; the prognosis is definitely better than in ovarian carcinoma, the recurrences occurring much later. These tumors are especially radiosensitive.

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A ROENTGENOLOGIC STUDY OF THE MECHANISM OF ENGAGEMENT OF THE FETAL HEAD*

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O UR first communication relevant to the causes of ease or difficulty in labor was directed to a detailed description of the anatomic variations in female pelves and their classification.[1] This analysis of pelvic form represented an attempt to make practical use of the results of anatomic and anthropologic observations since anatomists and anthropologists have long been cognizant of the salient characteristics of the four parent types as described by us, i.e., the gynecoid, android, anthropoid, and platypelloid (flat) forms.

In a more recent publication[2] we further applied these anatomic principles in the classification of the pelvic form in 215 primigravid women by means of roentgenologic methods. At that time in addition to the statistical data concerning the frequency of occurrence of these pelvic types in living women, attention was directed toward the recognition of intermediate forms and also the factors which appear to influence the shape of the pelvic architecture.

This present investigation deals with the mechanism of engagement of the fetal head with respect to the shape of the inlet in 200 unselected gravid women. The observations herein reported have been derived from the interpretation of at least one set of stereoroentgenograms obtained as early in labor as possible. Throughout this investigation we have made use of the precision stereoscope for viewing the stereoroentgenograms, and we feel enthusiastic over its practical usefulness. Although the films may be viewed through the ordinary stereoscope found in all x-ray laboratories, the precision instrument is superior in every respect since distortion in the size and shape of the image is corrected. While the optical principles have been previously reported by one of us,[3] it may be pertinent to describe briefly the advantages offered by such an instrument. Any obstetrician will grant the diagnostic value of a procedure which would permit him to visualize clearly the presenting part and the maternal pelvis at term or during labor bearing the same size, shape, and relationship to each other as would be observed by his own eyes held approximately 10 inches perpendicularly above the pelvic

region of the woman in labor. Such an ideal objective is made possible by the precision stereoscope. By the use of any standard technic of stereoroentgenography, two enlarged shadow images are cast by the roentgen ray on the film. When these two films are placed in the stereoscope, the obstetrician may study an exact duplicate of the fetal pelvic relationships which obtained in the living women at the time the exposures were made. In an emergency this procedure may be carried out within an hour, thereby revealing the great practical possibilities offered by such a simple but accurate diagnostic method.

Frequently lateral films were obtained in order to study the fetal pelvic relationship from the lateral aspect. These films reveal the relationship of the fetal head to the inclined inlet, the promontory, and the symphysis, and hence are most suited for a study of the mechanism of engagement.

Although, as a rule, one roentgenologic examination alone was obtained in the average case, we were impressed with the ease by which stereoroentgenograms could be taken during any stage of labor. In view of this fact, we believe that all cases of difficult labor warrant such an examination with immediate interpretation of the films before resorting to operative interference.

In order to standardize the statistical data concerning the relationship of the shape of the inlet to the position of the fetal head, all pelves were classified according to the nearest related prototype as gynecoid, android, anthropoid, or platypelloid (flat). Within each group variations in size and intermediate forms which possess a posterior segment characteristic of that type and a fore pelvis more typical of another may occur. These two factors may vary the mechanism of labor somewhat from the expected mechanism for the classical examples of each of the four groups as originally described by us.[1] This effect is not sufficiently marked to change the characteristic trend of the data for each of the four typical groups.

In view of the fact that this series of 200 unselected cases consisted largely of white primiparas, the possible effect of parity and race is not considered. Likewise, because of its infrequent occurrence, statistics on the platypelloid or flat type are not included.

OBSERVATIONS

The transversely placed head is easily recognized, and this may be called the true occipitotransverse position. Similarly, the true occipitoposterior or anterior positions, as well as the direct occipitoanterior, offer no difficulty in diagnosis when viewed through the stereoscope. The occiput in a small number of cases is found slightly anterior or posterior to the precise transverse diameter of the inlet, and these positions have

been called ''anterior'' or ''posterior tendencies'' and are listed as such in Tables I to IV. We have considered it advisable, in view of the fact that these positions approach the transverse more closely than the oblique diameters, to include them in the large group of transverse positions. Yet it must be recalled that these positions show a tendency to rotate posteriorly or anteriorly as the head descends. Since this investigation is limited to the engagement of the head at the inlet, the ultimate position assumed by the head at or below the midpelvis is not discussed at this time.

TABLE I. ENGAGEMENT IN THE GYNECOID (NORMAL) TYPE BASED ON 81 CASES

	NO. OF CASES	PER-CENTAGE		NO. OF CASES	PER-CENTAGE	TOTAL (PER-CENTAGE)
R.O.P.	2	2.5	L.O.P.	6	7.5	10
R.O.T. tending to R.O.P.	2	2.5 ⎤	L.O.T. tending to L.O.P.	5	6.0 ⎤	
R.O.T.	18	22.0 ⎬ 27	L.O.T.	26	32.0 ⎬ 42	69
R.O.T. tending to R.O.A.	2	2.5 ⎦	L.O.T. tending to L.O.A.	3	4.0 ⎦	
R.O.A.	9	11.0	L.O.A.	7	9.0	20
Direct O.A.	1					1
Right Position	33	40.5	Left Position	47	58.5	

In the gynecoid or typical female pelvis left positions of the occiput occur more commonly than right (58.5—40.5 per cent). The greater frequency of left positions is due to the larger number of L.O.T. and L.O.P. positions (Table I). Absolute transverse positions were noted in 54 per cent, and when the posterior and anterior tendencies are included, transverse positions reach the high incidence of 69 per cent. Although oblique positions are fewer in number (right, 11.5 per cent; left, 18.5 per cent), the left oblique offers a more favorable diameter for the fetal head than the right in the normal pelvis. Anterior positions, including one direct occipitoanterior, were slightly more than twice as common as posterior positions (21 per cent—10 per cent).

Again, in Table II we observe that left positions greatly exceed the right, a fact due to a greater number of L.O.P. and L.O.T. positions.

TABLE II. ENGAGEMENT IN THE ANDROID (MASCULINE) TYPE BASED ON 59 CASES

	NO. OF CASES	PER-CENTAGE		NO. OF CASES	PER-CENTAGE	TOTAL (PER-CENTAGE)
R.O.P.	8	13.5	L.O.P.	4	7.0	20.5
R.O.T. tending to R.O.P.	0	--- ⎤	L.O.T. tending to L.O.P.	5	8.5 ⎤	
R.O.T.	7	12.0 ⎬ 15	L.O.T.	25	42.5 ⎬ 56	71.0
R.O.T. tending to R.O.A	2	3.0 ⎦	L.O.T. tending to L.O.A.	3	5.0 ⎦	
R.O.A.	1	1.5	L.O.A.	4	7.0	8.5
Right Position	18	30.0	Left Position	41	70.0	

Transverse positions of the occiput were noted in 71 per cent of the cases when the anterior and posterior tendencies were included, but the absolute transverse alone occurred in 54.5 per cent of the cases. In contrast to the gynecoid or normal pelvis, right oblique positions exceed the left by 5 per cent.

Although transverse positions are almost three times more common than the combined anterior and posterior positions, we note the effect of the pelvic type on engagement by the greater number of posterior positions and a corresponding decrease in anterior positions of the occiput (20.5 per cent—8.5 per cent). Thus, android types definitely predispose to posterior positions. This fact has been suggested before by Thoms,[4] Taylor,[5] and others.

Table III reveals interesting findings in relation to this characteristically long narrow inlet. Note that the number of transverse positions

TABLE III. ENGAGEMENT IN THE ANTHROPOID TYPE BASED ON 59 CASES

	NO. OF CASES	PER-CENTAGE		NO. OF CASES	PER-CENTAGE	TOTAL (PER-CENTAGE)
R.O.P.	9	15	L.O.P.	8	13.5	28.5
R.O.T. tending to R.O.P.	3	5 ⎫	L.O.T. tending to L.O.P.	5	8.5 ⎫	
R.O.T.	4	7 ⎬ 14	L.O.T.	6	10.0 ⎬ 23.5	37.5
R.O.T. tending to R.O.A.	1	2 ⎭	L.O.T. tending to L.O.A.	3	5.0 ⎭	
R.O.A.	3	5	L.O.A.	7	12.0	17.0
Direct O.A.	10	17				17.0
Right Position	20	34	Left Position	29	49.0	

has decreased markedly to 37.5 per cent. Even this may seem an unexpectedly high incidence for this type of pelvis, but it must be recalled that intermediate forms possessing ample transverse diameters were included in this group. Or an original transverse position may be found early in labor, rotation occurring posteriorly or anteriorly with descent. The anterior and posterior positions have definitely increased—28.5 per cent for the posterior type and 34 per cent for oblique anterior and direct occipitoanterior positions. The frequent occurrence of the directly anterior occiput (17 per cent) represented one of the most interesting and unexpected findings in the investigation.

Thus it may be definitely stated in agreement with Fabre and Trillat,[14] Thoms,[4] and others that the anthropoid type of pelvis predisposes to posterior positions. We would like to point out, however, that anterior positions, particularly the direct occipitoanterior, are also decidedly characteristic of this type. In fact, the number of cases in which the occiput was found in the midline behind the symphysis equalled the combined anterior oblique positions.

From reference to Table IV, it is instructive to note that the occiput is directed to the left in 59 per cent of the cases and to the right in 35.5 per cent in this series. (Direct occipitoanterior position 5.5 per cent.) These results are in accord with the accepted opinion regarding this

TABLE IV. ENGAGEMENT WITHOUT REGARD TO TYPE BASED ON 200 CASES

	NO. OF CASES	PER-CENTAGE		NO. OF CASES	PER-CENTAGE	TOTAL (PER-CENTAGE)
R.O.P.	19	9.5	L.O.P.	18	9.0	18.5
R.O.T. tending to R.O.P.	5	2.5 ⎫	L.O.T. tending to L.O.P.	15	7.5 ⎫	
R.O.T.	29	14.5 ⎬ 19.5	L.O.T.	57	28.5 ⎬ 40.5	60.0
R.O.T. tending to R.O.A.	5	2.5 ⎭	L.O.T. tending to L.O.A.	9	4.5 ⎭	
R.O.A.	13	6.5	L.O.A.	19	9.5	16.0
Direct O.A.	11	5.5				5.5
Right Position	71	35.5	Left Position	118	59.0	

point. Plass,[6] for instance, from a series of 635 labors, reports the occiput to the left in 64 per cent and to the right in 36 per cent, as recognized by abdominal and vaginal examination.

The transverse positions by far exceed all others, occurring in 60 per cent of the cases. While anterior positions, including the direct occipitoanterior, occurred in 21.5 per cent, the posterior positions approach this number very closely so that one may be permitted to suggest that posterior positions at the inlet occur as frequently as anterior types, each approximately 20 per cent, when the pelvic shape is not considered.

Right and left oblique positions in this combined table are approximately equal with regard to incidence of occurrence so that the rectum and sigmoid encroach on the left oblique to a negligible degree.

DISCUSSION

The diameter of the inlet most commonly selected by the fetal head in the act of engagement has remained a matter of dispute for two centuries. Prior to the eighteenth century the head was believed to engage in the conjugate diameter. At that time Sir Fielding Ould[7] suggested the greater frequency of transverse positions of the occiput. Almost simultaneously Saxtorph[8] and Solaryes[9] advocated the theory that the oblique diameters rather than the transverse were more favorable for the head, especially the right. At the present time, most authorities accept this latter view, believing that transverse positions represent a passing stage in the act of anterior rotation of an occipitoposterior position. Many of the older authorities failed to mention the occurrence of the transverse position. In 1916, Plass[6] recognized transverse positions in 21.8 per cent of his cases and aptly questioned the more generally accepted theory concerning the supposed prevalence of oblique positions by stating, ''If it is admitted that the sagittal suture is some-

times transverse while the head is at the brim, we must either believe in high rotation or original transverse engagement and the latter idea seems more tenable.'' DeLee[10] from clinical experience believes that the transverse position occurs frequently. Our own clinical experience previous to this investigation also supported this view.[11]

Before the advent of the roentgen ray as a diagnostic method, the older authorities rarely considered the influence of the pelvis on the position of the head at engagement. During the early part of the present century, there was an increasing appreciation of the importance of the pelvis in the causation of occipitoposterior positions. Within recent years the contributions of Thoms are especially noteworthy in this regard. While it is true that this present series of 200 cases is small compared to the larger series on which others have based their conclusions, the accuracy of the roentgenologic method used for the recognition of position and the associated pelvic type makes these observations particularly significant.

In order to summarize the results listed above in Tables I to IV and to reveal more clearly the influence of the shape of the pelvis on the position of the head at the inlet, Table V has been arranged.

TABLE V

	GYNECOID	ANDROID	ANTHRO-POID	COMBINED
Posterior oblique position	10	20.5	28.5	18.5
Transverse position	69	71.0	37.5	60.0
Anterior oblique position	20	8.5	17.0	16.0
Direct occipitoanterior position	1	----	17.0	5.5

It will be observed that transverse positions in the gynecoid and android types occur in approximately 70 per cent of the cases. This finding is not unexpected when it is realized that these types characteristically possess a wide transverse diameter which is not encroached upon by the promontory to the extent ordinarily believed. The increase in the number of posterior positions and decrease in anterior positions in android types are also quite definite. As previously mentioned by us,[1] the tendency on the part of the head to assume a posterior oblique position may be attributed to the narrow fore pelvis so typical of masculine forms.

As the shape of the pelvis approaches a long oval, the head shows a corresponding tendency to utilize the long inlet diameter. Thus in anthropoid types there is observed a decided increase in the number of posterior and anterior positions with a great decrease in the transversely placed head. As a matter of fact, unless the child is small, the head will be arrested if the transverse position is maintained in anthropoid types which are at all typical from an architectural standpoint. Hence the recognition of an anthropoid type during the antepartum

period permits the obstetrician to predict the possible occurrence of either a posterior position in labor or arrest of the head if an original transverse position persists. Likewise, this unfavorable transverse position may be corrected by combined external and internal manipulation and labor shortened if an accurate diagnosis of position and pelvic type is made early in labor by use of the roentgen ray.

The observation that the directly anterior occiput occurred in 17 per cent of anthropoid types represents an important finding. This position of the occiput becomes characteristically associated with the long, narrow inlet. These positions occurred in anthropoid types possessing a well-curved ample fore pelvis, and it seems justifiable to state that, as a general rule, the size of the angle of the fore pelvis plays an important rôle in directing the occiput anteriorly or posteriorly.

The occiput rarely, if ever, encroaches upon the confines of the sacral area posteriorly at the inlet. A direct occipitoposterior position at a high level was not observed in this series. Undoubtedly, the explanation can be attributed to the prominence of the maternal lumbosacral region. Even in the most marked obliquely posterior positions, the head rested comfortably in the trough on either side of the lumbovertebral column. In this event the occiput was placed opposite the sacroiliac synchondrosis and only a portion of the medial aspect of the head became directly related to the extremity of the sacral alae of the first sacral vertebra.

THE POSITION OF THE FETUS AS RELATED TO THE PELVIC INLET

For practical purposes the common position assumed by the head at rest in the inlet may be divided into three classes:

1. Primary transverse positions. This group includes the true transverse position and the posterior and anterior tendencies.

2. Primary posterior positions. The sagittal suture occupies one of the oblique diameters with the occiput directed posteriorly.

3. Primary anterior positions. In this group are included the oblique anterior and the direct occipito anterior positions.

THE PRIMARY TRANSVERSE POSITION

Attention is first directed to certain peculiarities in the attitude of the fetus. We are indebted to Warnekros[12] for the first careful description of changes in the attitude of the fetus as revealed by the roentgen ray. The child's back as recognized by the fetal vertebral column is well curved, occupying one lateral segment of the uterus with the small parts suitably disposed in the opposite segment (Fig. 1). In this relaxed state the fetal spine is always directed at an appreciable angle toward the inlet, a point also clearly shown in Fig. 1. This relationship is usually maintained during descent and, we believe, becomes an important factor in assisting rotation, as will be shown later. The long occipitofrontal axis of the child's head assumes a position at right angles to the cervical portion of the fetal spine and the head seems to overhang the obliquely inclined inlet (Fig. 1). This position of the head frequently leaves the impression of good flexion with respect to the pelvis.

The posterior parietal bone sags into the inlet and becomes more easily palpable on vaginal examination. The sagittal suture points toward the symphysis. These features are more clearly shown in Fig. 4. Note that the posterior parietal eminence of the child's head is placed considerably below the sacral promontory, a position which is quite analogous to the well-known fact that in lower mammals the promontory is passed long before the fetus is confronted with the bony passage (Schumann[13]).

Varnier[15] in 1897 originally described this resting attitude of the fetal head which we have found to represent the most common position at the onset of labor even if the head is more deeply engaged. However, it will be readily understood that such a position predisposes to a high position of the fetal head. Moir's case[16] (shown in Fig. 2) of a woman dying in the later stages of labor is a particularly good example of the preservation of this normal parietal position of the fetal head

Fig. 1.—The resting primary transverse position (anterior view). Note the state of physiologic ease as illustrated by the curved spine and right-angled relationship to the long axis of the head. The head is resting across the inlet, well flexed with respect to the pelvis, the posterior parietal bone overhanging the inlet and the sagittal suture directed toward the symphysis.

in a case of obvious disproportion, although it is not quite true to life. This photograph clearly reveals the features described above and illustrated in Figs. 1 and 4. Note also that the long axis of the child is considerably posterior to the axis of the inlet and it illustrates that the child's head must undergo lateral flexion in order to fit squarely into the inlet.

The other well-known position referred to in obstetric texts was described by Naegele[17] in 1838 and has been called Naegele's obliquity. In such cases the sagittal suture is directed nearer the promontory, thereby permitting the anterior parietal bone to be felt on vaginal examination. We have not recognized a typical case of Naegele's obliquity and consider that it must represent a very rare form of engagement. A very dependent uterus with a relaxed abdominal wall would direct the fetal axis toward the inlet in such a fashion as to afford a possible example of

this type of presentation. As Williams[18] pointed out, Varnier's theory presupposes that the axis of the uterus is posterior to the axis of the superior straight; Naegele's theory suggests that it is placed in front of it. Williams contends that neither is quite true and believes that the long axis of the uterus approaches the axis of the superior straight when the uterus rises in the abdomen with contractions.

General Effect of Labor on the Fetus.—With the onset of labor we have noted that the child's body becomes progressively straighter with loss of the resting curvature, a point which is most characteristically seen in the straightening of the fetal vertebral column. (Compare Figs. 1 and 3.) In very active labor with strong pains the vertebral column may be truthfully termed the "poker spine" since it is

Fig. 2.—Moir's case of a woman who died suddenly late in labor. Note that the sagittal suture is directed toward the symphysis and the posterior parietal bone over-hangs the inlet below the promontory. This illustrates the persistence of a normal position in a case of fetal pelvic disproportion. Courtesy of C. Moir and J. Obst. & Gynec., Brit. Emp.

frequently observed as a straight line. Even when the head is low in the pelvis, the angle toward the inlet is maintained except in those instances in which the uterus deviates abnormally toward the side opposite the fetal spine. The degree of curvature or straightness in the fetal spine early in labor is to a large extent dependent on the presence or absence of amniotic fluid. The amniotic fluid tends to cause a diffusion of the forces secondary to the uterine contractions according to the laws of fluid pressure. Hence, the most marked straightening of the vertebral column is noticeable after the membranes rupture or in cases with a scant amount

of fluid. The subsequent flexion at this level ordinarily attributed to labor is also largely dependent on the presence or absence of amniotic fluid. If membranes are preserved and if an ample amount of forewaters is present, the fetal head shows little change from the resting position (Fig. 1) even after some descent into the pelvis has occurred. If the fetal head fits closely into the cervix or if membranes rupture early, the head becomes confronted with the resistance of the cervix and flexion follows. But the most characteristic sign that labor is in progress, other than the straightness noted in the vertebral column, is the overlapping of the fetal bones (Fig. 3). Overlapping is particularly noticeable at the coronal suture and the frontal bones are usually depressed below the parietals at this point. Less marked but definite overriding may be observed at the lambdoidal suture. The frontal bones rarely, if ever, show this tendency at the frontal suture in a normal living fetus.

That the tense soft parts of the lower uterine segment and cervix are chiefly responsible for the overlapping and molding and flexion of the head seems con-

Fig. 3.—Effect of labor on the attitude of the fetus. Note that rather marked overlapping of the skull bones with a well-flexed head and a straight spine has occurred high above the pelvic inlet. Membranes ruptured.

clusive because of the unexpected observation that these changes in the head may occur high above the inlet before the boundaries of the true pelvis could exert an influence. An attempt has been made to reveal this observation in Fig. 3. The stereoscopic view of this head, showing flexion and marked overlapping of bones, revealed that its situation was high above the bony inlet.

Engagement of the Fetal Head.—One of the most interesting and consistent observations made in the series under discussion pertained to the method by which the fetal head entered the pelvis from this so-called primary transverse position with the onset of contractions. In 60 per cent of the cases the head was noted in the transverse or just off the transverse, either slightly anterior or posterior. It has been repeatedly stated in the textbooks that such a position at the inlet is uncommon. The point seems to have been missed that there is a considerable obliquity of the plane of the pelvis and that the axis of the uterus or child, as Varnier observed, is not perpendicular to this plane but is posterior to it so that the fetal

head actually descends below the promontory before it is met by the symphysis pubis. While this point has been referred to above, the repetition is justified in order to illustrate that, for descent to occur from this resting position, *the anterior parietal bone must slip behind the symphysis while the posterior parietal remains relatively fixed at or below the promontory*. As it descends in this manner the head tends to fit more and more squarely into the transverse diameter until the usual appearance of the head in midpelvis is noted (Fig. 6). Three stages in the act of engagement from the parietal position at the inlet to the squarely fitting engaged head may be visualized to better advantage by a study of Figs. 4, 5, and 6.

Fig. 4 illustrates the resting parietal position with the posterior parietal eminence placed at a low level with respect to the promontory and the median sagittal suture directed toward the symphysis. A more advanced stage of engagement is shown in Fig. 5. It will be noted that the anterior parietal bone is tending to slip downward behind the symphysis with the posterior parietal portion of the head remaining relatively steady against the upper sacral region. Slight lateral flexion of the child's head on its body is noticeable. Complete engagement with the head in midpelvis is illustrated in Fig. 6. The head is now fitting squarely in the bony pelvis and between contractions rather marked lateral flexion of the child's head may be observed. This is due to the more posterior position assumed by the fetal axis when the contractions subside. These three stages in the act of engagement are combined in one diagram in Fig. 7 and the slipping downward of the anterior parietal bone behind the symphysis may be observed to better advantage.

Roentgenograms from many patients at term and in labor are necessary to reconstruct this mechanism of engagement since the head may or may not have already executed a part of the act. The appearance of the head in the first stage of engagement (Fig. 4) will be observed only when the head is high at or above the inlet at the onset of labor. Its frequency of occurrence may be judged by the number of unengaged heads found at the onset of labor. Williams was aware of this fact since he contended that Varnier's position as described obtained only when considerable disproportion existed between the size of the head and the pelvis. (See Moir's case, Fig. 2.) In the light of these studies this high parietal position of the head is more frequently noted and disproportion is by no means the sole cause. It may be held in this high position by firm soft parts, but its persistence long after the onset of labor is distinctly pathologic. We have a number of actual cases to illustrate this point, but a discussion of this problem is beyond the scope of the present investigation and will be reserved for more detailed consideration in a subsequent article. The more frequent position from which the act of engagement begins is illustrated in Fig. 5. This position may be primary in any individual case at the beginning of labor or may represent a passing stage of the head which originally presented higher as in Fig. 4.

This act of engagement may be followed by abdominal examination if the head is found floating at term. The abdominal hand when grasping the head in the position shown in Fig. 4 overrides it, and an impression is left that the head is lower in the pelvis than is actually the case. With the onset of labor the succeeding two stages are enacted, and the head undergoes lateral flexion to fit squarely into the inlet. When this occurs, the brow becomes more easily felt abdominally.

This act, so to speak, is the reverse of the mechanism referred to as synclitism which is clearly illustrated in Fig. 8 and which represents the principles of engagement as generally accepted and taught at the present time. Briefly, the mechanism described and illustrated above is somewhat similar to the mechanism of the posterior parietal presentation discussed in most obstetric texts with reference to the contracted pelvis. We merely wish to point out that from this investigation we are led to accept this mechanism as the common and usual method of engagement.
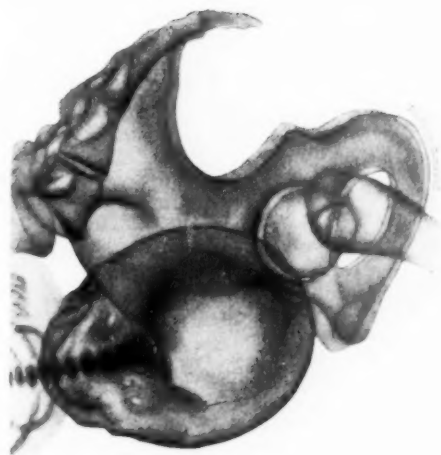
Fig. 6.
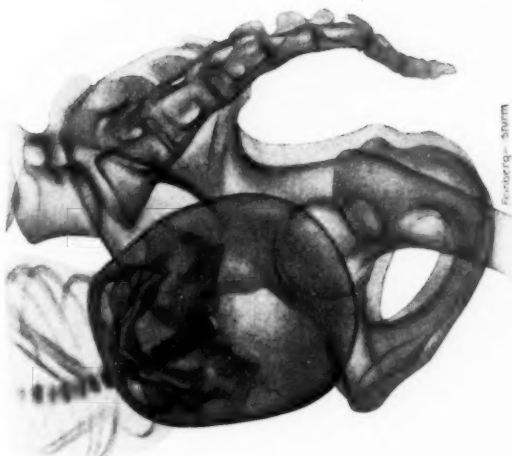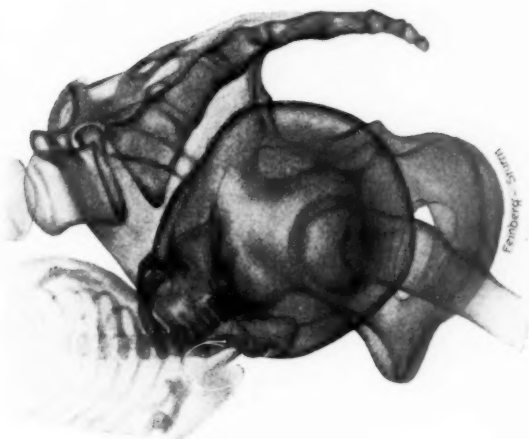
Fig. 5.

Fig. 4.

Fig. 4.—Lateral view of resting transverse position. Note that the head is directed toward the symphysis. The parietal eminence is considerably below the sacral promontory.

Fig. 5.—Lateral view of the partially engaged head. The anterior parietal above is slipping behind the symphysis and the head is tending to fit more squarely in the inlet. Note the beginning lateral flexion of the child's head.

Fig. 6.—Lateral view of the engaged fetal head. The anterior parietal bone has slipped behind the symphysis and the head is fitting squarely in the pelvis. Note the definite lateral flexion of the head.

It would seem natural from the foregoing facts that the reverse synclitism or the sliding of the head behind the symphysis would be greatly aided by the upright posture. This would bring the axis of the uterus more nearly parallel with the axis of the superior straight and aid in the rocking of the head into the inlet. Hence, the upright posture anatomically assists engagement of the fetal head.
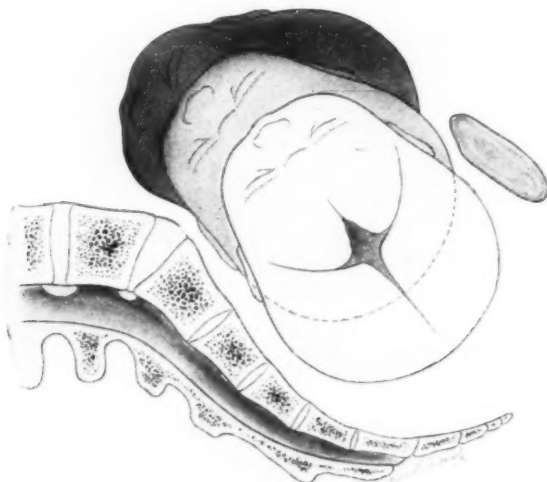
Fig. 7.—The mechanism of engagement as revealed by this investigation.
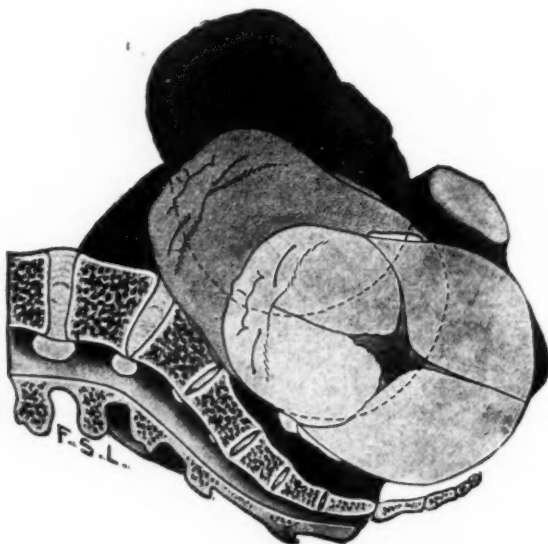
Fig. 8.—Synclitism. Illustrating the present accepted principle of engagement.

THE PRIMARY POSTERIOR POSITION

As a rule, the head may be found in this position not only at the beginning of labor but also at any time during the last month of pregnancy, and the pelvis usually conforms to the android or anthropoid type suggesting that the shape of the soft parts has changed in conjunction with the bony pelvis to allow this fetal pelvic

adaptation to occur. But it is not unusual to find a high head in the transverse parietal position described above in typical anthropoid types, fetal pelvic adaptation to a posterior or anterior position occurring soon after the beginning of labor.

The appearance of the resting posterior position before or at the onset of labor is shown in Figs. 9 and 10. The front view, Fig. 9, shows that the fetus rests at ease with the spinal column adjacent to the posterior iliac portion of the inlet near the sacroiliac articulation. The fetal head, with its occiput directed toward the sacrosciatic notch, occupies one of the oblique diameters of the inlet and overhangs the inlet in a manner which is comparable to the condition of affairs described above for the transverse resting position. In other words, although the head is placed at right angles to the cervical spine and appears flexed with relation to the pelvis, it is nevertheless directed toward the symphysis and the anterior fontanel is located high behind the symphysis to the right or left of the midline. The curved attitude of the fetus characteristic of the child in a state of physiologic ease is also present. These features may be noted to better advantage in Fig. 10 from the lateral aspect.

The onset of labor immediately introduces the question of anterior rotation or the persistence of the original position with the tendency to rock posteriorly into the hollow of the sacrum. This latter feature seems secondary to the gripping of the head by soft parts or by changes in the shape of the pelvic architecture at lower levels.

While it is beyond the scope of the present investigation to enter into a discussion of the various theories concerning the causes of rotation, many of which are of a controversial nature, we feel justified only in suggesting those factors which may lend understanding to the facts noted in the stereoscope. The first theory has recently been reviewed and emphasized from observations on mammals and humans by Rudolph and Ivy,[19] and in their opinion it refers essentially to the intrinsic action of the uterus as a rotator of the child's body. The shape of the uterus undoubtedly plays an important rôle as suggested by Olshausen.[20] Bumm,[21] accepting Olshausen's explanation, introduces another important factor substantiated by our observations. Paramore[22] quotes Bumm as follows: "It is the trunk which institutes the anterior rotation and imparts to the occiput the impulses which cause it to rotate in the same direction." Paramore continues as follows: "The rotation of the fetal trunk is determined by the projection forward of the maternal vertebral column; this prevents the fetal back from turning completely behind and, combined with the effects of the uterine contractions, causes it first to become lateral and finally anterior. In this rotation the fetal trunk carries the occiput with it."

We believe that the influences concerned with rotation discussed above may be greatly assisted by two factors which have been consistently observed through the stereoscope in this investigation.

We have already referred to the angle of the fetal axis toward the inlet. This angle is quite definite in Fig. 11, which reveals the transverse stage in the rotation of a primary posterior position. The second factor concerns the inclination of the inlet to the maternal vertebral column. This obliqueness is particularly noticeable in anthropoid types in which posterior positions are prone to occur. In these types the inlet is very nearly perpendicular to the horizontal in the upright posture. A third factor to consider is the very obvious one that the pelvic brim is bounded anteriorly by the yielding abdominal wall and posteriorly by the fixed maternal hard parts. These three factors bring about a state of affairs in which a moving body is directed tangentially toward a plane that is inclined downward and a forward spiral movement takes place in the line of least resistance. This rotation may occur at varying levels above the pelvic floor or the original position may persist, particularly if some secondary factor in the pelvic architecture exists, until the mus-
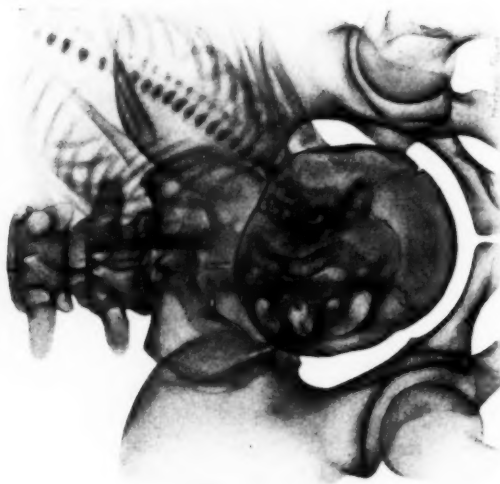
Fig. 11.
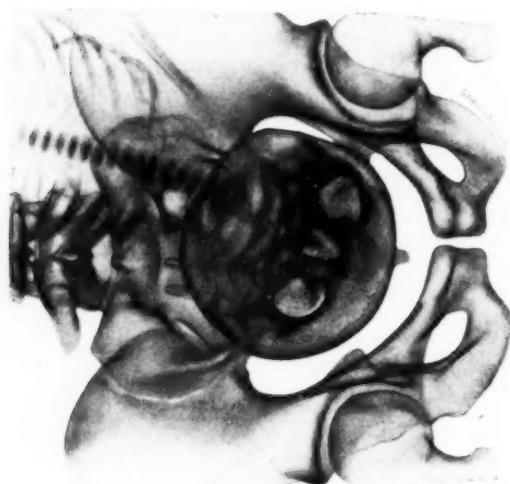
Fig. 10.

Fig. 9.

Fig. 9.—The primary posterior position before the onset of labor (anterior view).
Fig. 10.—The resting primary posterior position as viewed from the lateral aspect.
Fig. 11.—Spontaneous rotation of the case shown in Fig. 9. The head is placed transversely above the level of the ischial spines. Note that the axis of the child is inclined toward the oblique inlet and that the line of least resistance is anterior.

cular pelvic gutter is reached. Again, the lower pelvic factors which may prevent or assist in rotation of the head, such as the shape of the lower pelvic architecture or the grip of the soft parts, create a problem in themselves which must be reserved for further investigation.

THE PRIMARY ANTERIOR POSITION

In this group are included the oblique anterior positions and the directly anterior occiput. The recognition of this latter position in itself was an unexpected finding but the relative frequency of occurrence of this supposedly rare position, namely 5.5 per cent in the series as a whole, represents a most interesting observation. It is almost invariably found in association with a large but typical anthropoid type
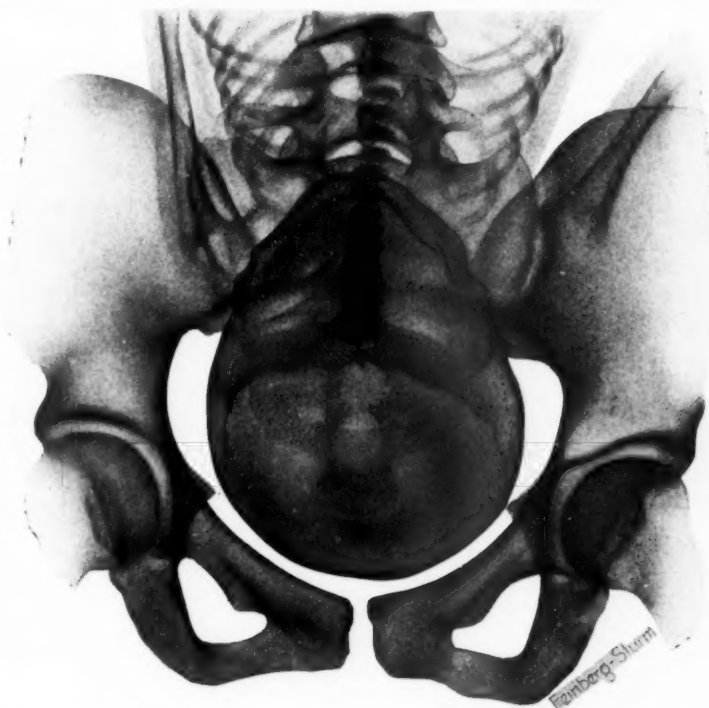
Fig. 12.—Primary direct occipitoanterior position (anterior view).

of pelvis possessing an ample angle in the fore pelvis. Unfortunately, only three cases had received a complete roentgenologic examination in the last month of pregnancy, in addition to the x-ray pictures during labor. In these cases the occiput was directed anteriorly at this early date and relatively low in the pelvis at that time as well as at the onset of labor. The appearance of this position from the anterior and lateral aspect is illustrated in Figs. 12 and 13. In the resting position before the onset of labor, the head is overhanging the inlet with the occiput directed toward the symphysis in a manner comparable to the resting head as described for the primary, transverse and posterior positions. The sagittal suture occupies the mid anteroposterior diameter of the inlet, and the frontal region of the head is close to the promontory or fits into the anterior concavity of the sacrum.

Presumably, the head passes from inlet to outlet in this position. Engagement is effected by the descent of the occiput in the midline behind the symphysis. Flex-

ion as a rule is not marked at any time in any position of the pelvis. If present, the degree appears to be dependent on the diameter of the long axis of the head as compared to the length of the anteroposterior diameter of the pelvis. Hence, in a directly anterior position, as in any other position, the head retains its right-angle relationship to the spine unless resistance is offered below.

Obstetrically no great difficulty was encountered in these cases. It may be recalled that prior to the time of Sir Fielding Ould it was the accepted theory that the head entered the inlet in this directly anterior position. Within recent years this old teaching has been revived by McKerron[23] and others, although Williams and DeLee are inclined to consider these positions to be rare and distinctly pathologic. Yet, according to our observations, ten examples were found in a series of 59 anthropoid types, and one was noted in a normal gynecoid pelvis. It is also im-
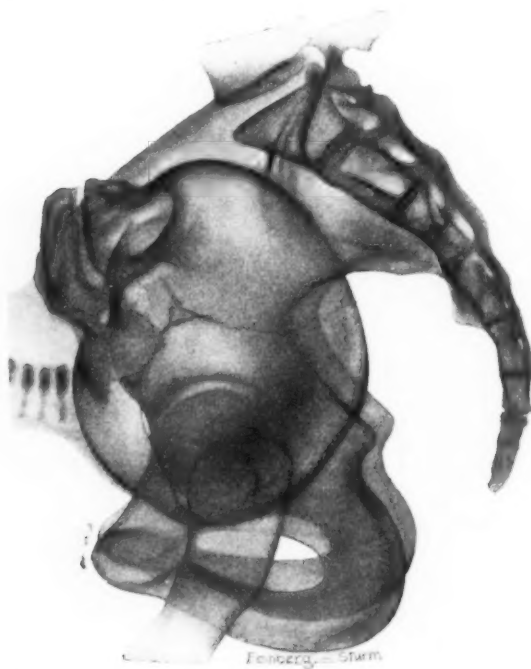
Fig. 13.—Primary direct occipitoanterior position (lateral view).

portant to remember that the direct occipitoanterior position is intimately associated with the anthropoid type of pelvis which, along with the conformation of the soft parts, represents the causative factor.

SUMMARY

1. The roentgen ray, interpreted by the precision stereoscope, offers a distinct refinement in obstetric diagnosis during labor. This method is rapid, accurate, and practical. All examples of atypical labor warrant a roentgenologic examination with immediate interpretation of the films before resorting to operative interference.

2. Statistics on positions of the head at the inlet in relation to the pelvic type have been tabulated.

3. Positions at the inlet may be divided into three classes: (a) primary posterior positions, (b) primary transverse positions, and (c) primary anterior positions including the direct occipitoanterior.

4. The transverse parietal position represents the common position at the onset of labor.

5. The act of engagement of the fetal head has been described. This act is the reverse of the principle known as synclitism hitherto accepted as the common method of engagement.

6. Posterior rotation is assisted by the angle assumed by the fetal axis along the slope of the uterine wall toward the inclined inlet. The uterine contractions impart a spiral movement to the body along these two inclined planes, and rotation forward along the line of least resistance takes place.

7. The attitude of the fetus at rest and the changes secondary to the onset of labor have been described.

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THE PRESENT-DAY TREND IN THE TREATMENT OF FIBROIDS OF THE UTERUS*

An Analysis of the Statistics of the Michael Reese Hospital During the Past Eleven Years

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THERE is no more fascinating study for the clinician in the field of therapy than the trends which manifest themselves from time to time. This is well exemplified in the analysis presented herewith of the treatment of fibroids of the uterus in the Department of Gynecology of the Michael Reese Hospital.

During the past eleven years ending Jan. 1, 1934, there were 1,001 patients who were treated for fibroids of the uterus. This includes both general ward and the private clientele of the various members of the department. Complete latitude of choice existed in the handling of the private patients and a comparable degree of freedom of choice in the rotating service in charge of the general ward. An analysis of the trends indicates a similarity of conclusion throughout the group.

The standard treatment for fibroids was surgical removal until the advent of radium. The enthusiasm with which radium was employed lasted until the department was forced to the conclusion that a panacea had not been found. Surgical removal began to displace radium gradually but definitely.

In the course of the analysis of the case records of these thousand patients, data were obtained bearing on correlated and equally interesting problems in the story of fibroids. These data related to such topics as the etiology of fibroids, the relation of fibroid pathology and malignancy, the association of ovarian and tubal pathology with sterility and fertility, the question of the normal duration of menstrual activity, the interpretation of the types of bleeding, and the alleged connection between hypertension and the myoma heart. The trend in treatment is analyzed and the shift justified. Mortality and complications are presented.

Etiology.—In a consideration of etiology it is curious to observe that the oldest and the newest concepts revolve around the presence of inflammation. This was the Galenic philosophy based entirely on clinical observation. Recent publications (Witherspoon)[23, 24] aim to prove that fibroids arise from the effect of ovarian hormonal dysfunction, the result of long-standing pelvic inflammation. Analysis of adnexal pathology as-

sociated with the fibroids removed by operation in this series fails to bear out this theory.

In this analysis the following types of ovarian pathology were found in association with fibroids: follicle cysts, 244, or 26.1 per cent; corpus luteum cysts, 129, or 13.7 per cent; dermoid cysts, 5 or 0.5 per cent; endometrioma, 11, or 1.2 per cent; multilocular cysts, 6, or 0.6 per cent; unilocular cysts, 1, or 0.1 per cent; and cystoma, 3, or 0.3 per cent. One or both ovaries were removed in 432, or 46.7 per cent, of the patients operated upon. Moreover, this group includes those patients in whom one or both ovaries were removed merely to facilitate removal of the fibroids or because of impairment of circulation. Witherspoon[24] reports having found salpingitis in 100 per cent of the negresses. In this series 214, or 19.9 per cent, of the patients showed associated unilateral or bilateral salpingitis. Pelvic adhesions were noted in 84, or 8.9 per cent, and one or both tubes were removed in 411, or 44.4 per cent. Hyperplasia of the endometrium was present in 211, or 22.4 per cent.

Fibroids are conceded to be an abnormal growth of hitherto normal myometrium. However, the thesis that this growth results from (a) a long-standing inflammatory disease producing (b) follicle cyst formation which in turn by a hyperestrinism results in (c) hyperplasia of the endometrium and (d) fibroid production, is not borne out by the infrequency with which these types of associated pathology were found in this series.

Pathology.—Microscopic study of the tumors removed in this operative series gave the following results: In 686 patients, or 73.1 per cent, the tumors were simple fibroids, the commonly accepted American designation. In some, fibrous tissue predominated, and in some, muscle tissue was in excess. For the purpose of this study no attempt was made to interpret this differentiation.

TABLE I. FIBROID PATHOLOGY, BASED ON 938 CASES

Fibromyoma	686	73.1%
Leiomyoma	7	0.7%
Adenomyoma	13	1.4%
Adenomyosis	70	7.5%
Degeneration	182	19.4%
Calcification	11	1.2%
Cartilage	1	0.1%
Infection	14	1.5%
Abscess	3	0.3%
Fibrosis	28	3.0%
Sarcoma	5	0.5%

In addition to this group of simple fibroids, there were 7 instances of leiomyoma (0.7 per cent) and 13 of adenomyoma (1.4 per cent). Adenomyosis of the uterus was found in 70 patients (7. 5 per cent).

Degenerative changes, either myxomatous or hyaline, occurred in 182 (19.4 per cent). Calcification was found in 11, or 1.2 per cent, and in-

fection of the fibroids was found in 14, or 1.5 per cent. In 3 of these patients there were frank abscesses. There were 28 patients (3.0 per cent) in whom there was fibrosis of the uterus in association with the existing fibroids, and there was one instance of cartilage formation in the presence of hyaline degeneration.

Associated malignancy of the uterus or malignancy developing in a fibroid is conspicuous by its paucity. In 5 patients the diagnosis of sarcoma occurring in a fibroid was positive in 4 and probable in one (0.4-0.5 per cent). There was no instance of carcinoma of the cervix. Carcinoma of the corpus uteri was found in 4 patients, an incidence of 0.4 per cent. Malignancy of the ovaries or tubes was not found.

The question of the development of sarcoma in fibroids has been studied intensively in many clinics. Lynch[14] in a review of 4,415 cases in the literature found approximately 2.0 per cent; Frankel[8] in a careful review of the material in the Peham Clinic found an incidence of 2.8 per cent, and Kermauner[13] reported exactly the same incidence from the other Vienna Frauenklinik. Evans[4] reported the finding of only 1.8 per cent in 4,000, and Keene[11] found only 0.8 per cent. Ewing[5] states that he has seen only 5 sarcomas developing in a fibroid of the uterus in twenty years. Albrecht[1] in a review of the literature reports the finding of 211 instances of carcinoma of the corpus uteri in a series of 9,990 women operated for fibroids of the uterus, an incidence of 2.1 per cent.

Changes in the endometrium entailing a huge list of descriptive terms were so completely clarified by Hitschman and Adlers' revelation of the physiologic cycle that one is prone to overlook the existence of a considerable variety in endometrial pathology. Witness the submitted list of diagnoses made by the excellent pathologists who studied the microscopic sections obtained from the uteri removed in this series.

TABLE II. PATHOLOGY OF THE ENDOMETRIUM, BASED ON 938 CASES
(SOME REDUPLICATION)

ENDOMETRIUM	NO.	PERCENTAGE
Glandular hyperplasia	112	11.9
Chronic endometritis	99	10.5
Subacute endometritis	7	0.7
Acute endometritis	3	0.3
Atrophy	59	6.3
Fibrosis	34	3.6
Polyps	71	7.6
Granular	30	3.2
Interstitial endometritis	33	3.5
Cystic	2	0.2
Edema	6	0.6
Decidua	15	1.6
Placenta	6	0.6
Carcinoma	4	0.4

A review of the associated ovarian pathology was of particular interest in the light of the newest concept of the etiology of fibroids and likewise in a consideration of the factors involved in the sterility ratio

of the patients in this series. The relation of ovarian pathology to the etiology of fibroids has been discussed. The significance of adnexal pathology associated with fibroids in an explanation of the occurrence of sterility will be considered subsequently in the paper.

TABLE III. PATHOLOGY OF THE OVARIES, BASED ON 938 CASES (42.4 PER CENT)—
(THERE IS CONSIDERABLE REDUPLICATION)

TYPE OF PATHOLOGY	NO.	PERCENTAGE
Follicle cysts	244	26.1
Corpus luteum cysts	129	13.7
Fibrosis	35	3.7
Chronic oophoritis	3	0.3
Tuboovarian adhesions	10	1.1
Endometrioma	11	1.2
Atrophy	6	0.6
Serous	9	0.9
Paraovarian	8	0.8
Multilocular	6	0.6
Unilocular	1	0.1
Cystoma	3	0.3
Inflammatory	3	0.3
Dermoid	5	0.5
Teratoma	1	0.1
Fibroma	1	0.1
Fibromyoma	1	0.1
Papillary cyst adenoma	4	0.4

The varieties of ovarian pathology are presented in Table III without comment. However, it should be noted that there is considerable duplication, different ovarian lesions frequently occurring in the same ovary.

Analysis of tubal pathology, as described elsewhere in the paper, indicates that tubal disease played a predominant rôle in the production of both absolute and relative sterility. The classification and frequency of tubal pathology is submitted in the accompanying table.

TABLE IV. PATHOLOGY OF THE TUBES, BASED ON 938 CASES (13.3 PER CENT)—
(VERY LITTLE REDUPLICATION)

TUBES	NO.	PERCENTAGE
Chronic salpingitis	27	2.9
Chronic adhesions, salpingitis, oophoritis	29	3.1
Chronic catarrhal salpingitis	36	3.8
Subacute catarrhal salpingitis	5	0.5
Acute catarrhal salpingitis	4	0.4
Acute perisalpingitis	4	0.4
Acute purulent salpingitis	2	0.2
Subacute salpingitis	4	0.4
Salpingitis isthmica nodosa	2	0.2
Hydrosalpinx	4	0.4
Pyosalpinx	4	0.4
Hematosalpinx	1	0.1
Endometriosis	1	0.1
Ectopic	1	0.1
Tuboovarian abscess	2	0.2
Tuberculosis	1	0.1
Adhesions	84	8.9

In this series the frequency of ovarian pathology in association with fibroids was found to be 42.4 per cent while the frequency of tubal path-

ology was decidedly less—13.3 per cent. In the literature most of the complications include adnexal pathology. Polak[20] recorded 54 per cent; Kelly and Cullen,[12] 35.6 per cent; McDonald,[16] 27.5 per cent; and R. T. Frank,[7] 18 per cent; while Keene and Kimbrough[11] specified a 44.4 per cent incidence of ovarian pathology. This is practically the same frequency as was found in this series.

Sterility and Fertility.—The relationship between fibroids and sterility continues to be a matter for investigation. Dr. L. E. Frankenthal, the senior attending gynecologist at Michael Reese Hospital, in a report of twenty-two years' experience with fibroids, published in 1911, stated that "the mechanical causes (of sterility in fibroids) obtain in a few cases only."[9] Graves[10] was of the opinion that any decrease of fertility in women with fibroids was either mechanical or abortive. Schreiner[22] reported sterility of 9.2 per cent of a series of 318 women. Albrecht concludes that fibroids are not responsible for sterility.

Among those who give high percentages of sterility associated with fibroids are Kelly and Cullen who in 1909 reported a sterility incidence of 33 per cent in women with fibroids; Phillips[19] in 1914, 29 per cent; Lynch and Maxwell[14] in 1922, 31.5 per cent; Keene[11] in 1930, 31.6 per cent; and Schmitz[21] in 1934, 36 per cent in nulliparas.

In this series there were 862 married women; the figures presented are based on this group only. Absolute sterility was present in 169 (19.6 per cent). The fertile group 693, or 80.4 per cent, included 60, or 6.9 per cent, whose pregnancies ended in abortion. The remaining 633, or 73.5 per cent, consisted of primiparas, 146, or 16.9 per cent; 192 para ii women, or 22.4 per cent; and 295 women who had three or more children, or 34.2 per cent.

TABLE V.   FERTILITY—STERILITY

	NO.	PERCENTAGE
Single	109	11.2
Married	862	88.8
Sterile	169	19.6
Fertile	693	80.4
Parous	633	73.5
Gravida 0, para 0	169	19.6
Gravida +, para 0	60	6.9
Para i	146	16.9
Para ii	192	22.4
Para iii+	295	34.2

It would seem from a study of the adnexal pathology in this series that the explanation of a large part of the sterility may be found in the coexisting tubal disease rather than in the presence of fibroids. In the sterile women 22.7 per cent showed tubal pathology. Those women whose pregnancies terminated in abortion had 24.1 per cent tubal disease, the primiparas, 19.5 per cent; paras ii, 9.5 per cent; and paras iii plus, 8.9 per cent.

In these various classifications ovarian pathology was fairly constant, ranging from 37.6 per cent to 49.4 per cent. Evidently in the 862 married women whose fertility was analyzed, tubal disease occupies a far

TABLE VI. RELATION OF ADNEXAL DISEASE TO FERTILITY AND STERILITY

	TUBAL PATHOLOGY	OVARIAN PATHOLOGY
Sterile	22.7%	40.4%
Abortive	24.1%	47.5%
Para i	19.5%	49.4%
Para ii	9.5%	40.5%
Para iii	8.9%	37.6%

more significant place in the production of sterility than is ascribable to either the presence of fibroids or the existence of ovarian pathology.

Menstrual Behavior.—The duration of menstruation has been studied intensively both in normal women and in women with fibroids. It has been stated that women who will subsequently develop fibroids are prone to menstruate early. In this series 129 (16.7 per cent) began menstruating at age twelve, 229 (29.7 per cent) at thirteen, and 172 (22.3 per cent) at fourteen, while only 13 (1.7 per cent) began at ten or under and 59 (7.6 per cent) at eleven. This ratio of frequencies compares with that of the figures given for normal series. It would seem to indicate that the individual in whom there is a tendency toward the development of fibroids does not have a precocious onset of menstruation.

TABLE VII. DURATION OF MENSTRUAL ACTIVITY

AGE OF ONSET	NO.	PERCENTAGE	PERCENTAGE MENSTRUATING TO 46 OR LATER
10 yr. and under	13	1.7	23.0
11 yr.	59	7.6	10.2
12 yr.	129	16.7	20.9
13 yr.	229	29.7	27.0
14 yr.	172	22.3	23.2
15 yr.	79	10.2	20.5
Over 15 yr.	91	11.8	35.1
Total	772	100.0	24.3

The statement is likewise made that the presence of fibroids causes a prolongation of menstrual activity. In this group 187, or 24.3 per cent, of the total were still menstruating at the age of forty-six. This is not a sufficient deviation from the normal figure to bear out the statement made above.

There is a problem in connection with duration of menstruation on which the figures obtained in this study do seem to throw some light. There are two opposing statements made regarding the span of menstrual activity: the one that women who have an early menarche have a late menopause and the other that the span is fairly constant, averaging from thirty to thirty-five years. In the patients of this group there

were 91 who did not begin to menstruate until sixteen or later. Of these women 35.1 per cent were still menstruating at the age of forty-six. Of the group who began menstruating at fifteen years or younger, only 22.7 per cent were still menstruating at forty-six. Apparently the span is fairly constant; those who have a late menarche tend to have a late menopause.

Symptoms.—The patients of this group exhibited the usual symptoms common to the presence of fibroids. These are listed in Table VIII.

TABLE VIII.   SYMPTOMS

SYMPTOMS	NO.	PERCENTAGE
Menorrhagia	469	46.9
Metrorrhagia	286	28.6
Pain	314	31.4
Backache	177	17.7
Dysmenorrhea	113	11.3
Abdominal enlargement	121	12.1
Bladder symptoms	114	11.4
Rectal symptoms	23	2.3
Gastrointestinal symptoms	32	3.2
Leucorrhea	12	1.2
Sterility	23	2.3
No symptoms	48	4.8

TABLE IX.   RELATION OF TYPE OF BLEEDING TO ADNEXAL PATHOLOGY

TYPE OF BLEEDING	OVARIAN PATHOLOGY								TUBAL STATUS		
	CYSTIC OVARY	CORPUS LUTEUM CYST	SALPINGO-OOPHORITIS	FIBROSIS	CYSTOMA	ENDOMETRIOSIS	NO PATHOLOGY	TOTAL	PATHOLOGY OF TUBE	NORMAL TUBE	TOTAL
Normal menstruation	88	44	11	11	4	4	208	370	31	279	310
Menorrhagia	79	38	13	12		1	154	297	29	211	240
Metrorrhagia	31	22	5	5	1	2	57	123	18	90	108
Menorrhagia	32	11	2	4			43	92	26	70	96
Decreased interval and menorrhagia	12	7	4	3			13	39	3	26	29
Irregular menses	8	6	2	2			16	34	2	22	24
Irregular menorrhagia	15	4	3			1	19	42	1	35	36
Postmenopausal bleeding	1						14	15		15	15
Continuous bleeding	4	1	1				7	13	1	9	10
Total	270	133	41	37	5	8	531	1025	111	757	860

An attempt was made to classify this group of patients according to the type of bleeding. Three hundred seventy patients had normal menses; 297 showed menorrhagia; 123, metrorrhagia; 92, a combination of menorrhagia and metrorrhagia; 39 exhibited a decreased intermenstrual interval; 34 were described as having irregular menses; 42 had irregular menstruation with menorrhagia; 15 showed postmenopausal bleeding; and 13 had continuous bleeding.

These various types of bleeding were figured against coexisting ovarian pathology in an attempt to determine a possible correlation. Classification of ovarian pathology included follicle cysts, corpus luteum cysts, tuboovarian inflammation, fibrosis ovarii, cystoma, and endometrioma.

It was not possible to establish any connection between the type of ovarian pathology and the kind of abnormal bleeding. It should be mentioned that 192, or 67.4 per cent, of the 270 patients with polycystic degeneration had some form of abnormal bleeding. Likewise 89, or 66.9 per cent, of the 133 patients with corpus luteum cysts had some form of abnormal bleeding.

The chief interest in the medical aspects presented by these patients lies in the cardiovascular findings. There were only 67, or 6.7 per cent, patients with organic heart disease. Sixty-one of these were either myocardial degeneration or hypertrophy, and 6 had rheumatic valvular lesions. Of these women 26 were from thirty-six to forty-five years of age while 37 were forty-six or over. Obviously the smallness of the total group and its occurrence in those decades in which fibroids commonly make their appearance confirms the generally accepted opinion (Graves,[10] Englemann,[3] Arkussky,[2] Peham[18]) that the relationship between heart disease and fibroids is merely coincidental. Analysis of the blood pressure findings in these women leads to the same conclusion. Systolic readings over 140 occurred chiefly in the older women. Readings over 150 were found in only 15.5 per cent of the entire series. Three-fourths of these women were over forty-five years of age.

TABLE X.   CARDIOVASCULAR DISTURBANCES

BLOOD PRESSURE	UNDER 26 (1.4)	26-35 (18.5)	36-45 (52.3)	46 AND OLDER (27.8%)	TOTAL
Under 111	30.8	11.8	13.1	5.8	11.1
111-120	30.8	30.8	19.0	13 2	19.7
121-130	30.8	35.3	24.8	15.6	24.4
131-140	7.6	14.8	18.3	17.0	17.1
141-150		5.5	13.5	15.2	12 2
Over 150		1.8	11.3	33.2	15.5
(Above percentages calculated within each age group)					100.0
O. H. D.		2	28	37	67
Rheumatic		2	2	2	6
Degenerative			26	35	61

Treatment.—The various procedures employed in the 1,001 patients during the eleven years covered by this study consisted of: supravaginal hysterectomy 663 times, myomectomy 122 times, vaginal hysterectomy 79 times, radium 73 times, total hysterectomy 49 times, and vaginal myomectomy 15 times. Table XI indicates strikingly the steadily increasing favor accorded to vaginal hysterectomy. Total hysterectomy remained about stationary in frequency until the last year during which almost

as many such operations were performed as during the preceding ten years. Supravaginal hysterectomy retained its position throughout the series as the operation most frequently chosen.

TABLE XI.   TREND IN TYPES OF TREATMENT

	TOTAL	1923	1933
Myomectomy	12.2	21.9	7.6
Vaginal myomectomy	1.5		
Supravaginal hysterectomy	66.3	56.2	57.6
Total hysterectomy	4.9	1.4	14.6
Vaginal hysterectomy	7.9	5.5	18.1
Radium	7.3	15.0	2.1

Among the 122 women in whom conservation was practiced by the performance of myomectomy, 81 were thirty-five years old or younger. On the other hand, it should be noted that in the later years of this series, particularly among women who had one or more children, the frequency of myomectomy in this younger age group has diminished by half in favor of supravaginal hysterectomy.

TABLE XII.   BEARING OF AGE ON CHOICE OF OPERATION

AGE IN YR.	MYOMEC- TOMY	VAG. MYOMEC- TOMY	SUPRAVAG. HYSTER.	TOTAL HYSTER.	VAG. HYSTER.	RADIUM
Under 36	66.4	33.3	16.7		1.3	2.7
36-40	20.5	13.3	27.7	18.4	17.7	19.4
41-45	4.1	20.1	27.6	46.9	45.6	30.1
Over 45	6.5	33.3	26.5	32.7	35.4	47.8
No age given	2.5		1.5	2.0		
Total Series	12.2	1.5	66.3	4.9	7.9	7.3

There was a small group (15) in whom vaginal myomectomy was performed for special indications.

The position of radium as a method of treatment for fibroids has shown a decided, though erratic decline. In 1923 radium was used in treating 15 per cent of all patients with fibroids, while in 1933 this type of treatment was used in only 2.1 per cent.

A consideration of the various methods of treatment with their advantages and disadvantages affords ample explanation for the trends noted above. Supravaginal hysterectomy remains the outstanding operation for this condition. Under ordinary circumstances it is the simplest and most rapid of the major operations. It rarely entails risk to bladder or ureters. When properly performed, it is practically bloodless. It insures complete removal not only of the existing tumors but of the potential tumor-bearing tissue. Convalescence is usually uncomplicated, and the mortality is exceedingly low. It permits of direct examination of the adnexa with the opportunity for such surgical treatment as their pathology may require and affords exploration of the abdominal cavity, including the appendix. It preserves the cervix in situ

which should serve as an anchorage for the vaginal vault and, if the endocervix is not entirely cored out, provides normal vaginal moisture and freedom from dyspareunia. It does away with the risk of a subsequent development of malignancy of the corpus uteri.

TABLE XIII. OPERATIONS ON ADNEXA, APPENDECTOMIES—BASED ON 937 OPERATIVE REMOVALS OF FIBROIDS

	NO.	PERCENTAGE
1 ovary	25	2.7
1 tube	4	0.4
Tube and ovary	219	23.9
2 tubes and 1 ovary	13	1.4
2 tubes and 2 ovaries	175	18.7
Appendix	270	28.8

Vaginal hysterectomy includes enough of these advantages, together with others peculiar to it, to insure its serious consideration by those competent to do it. In this operation the abdominal cavity is scarcely invaded, yet the adnexa may be surveyed. The cervix, lacerated, everted, hypertrophied, presenting nabothian cysts and erosions and carrying with it the questionable menace of a stump carcinoma is removed. In the woman who presents a relaxed birth canal, this operation permits of suitable repair in practically the same operative procedure and field. If asepsis and hemostasis have been satisfactory, convalescence should be as simple and uncomplicated as that following supravaginal hysterectomy. There are limitations in the selection of patients suitable for vaginal hysterectomy. It should not be employed when the tumors are larger than can be removed intact. Morcellement or bisection of the uterus is available but not desirable except in special instances. It is ill advised if the uterus is held fixed by heavy scars or the end-result of parametrial inflammation, or should it be employed when the corpus itself is fixed, nor in the presence of palpable adnexal pathology. It is likewise further contraindicated if there have been previous lower abdominal operations other than a simple appendectomy.

The advocates of total hysterectomy are vociferous in their claim that this operation should supplant supravaginal hysterectomy. Their position is based on the premise that carcinoma of the stump is a real menace and that in the hands of the competent gynecologist the procedure, while somewhat longer, should entail no greater morbidity or mortality. Thus far there has been no instance of carcinoma of the cervical stump observed in the clientele of the gynecologic ward or clinic of the Michael Reese Hospital. The infrequency of cervical carcinoma among Jewesses is only partially responsible for this observation since approximately one-third of our clientele is non-Jewish.

The statement that total hysterectomy carries no increased morbidity and mortality over supravaginal hysterectomy in trained hands is fully substantiated in this series; the major complications and mortality oc-

curred with other types of operations. Nevertheless, it should be emphasized that total hysterectomy demands a higher degree of operative skill and a more intimate knowledge of pelvic anatomy, both normal and distorted, than does supravaginal hysterectomy. Total hysterectomy is best suited for those patients in whom the vaginal route is contraindicated and in whom the pathology of the cervix is such as to require its removal.

Myomectomy, single or multiple, remains the operation of election primarily for those who desire offspring. It is likewise available for instances of single pedunculated tumors, with or without a twist of the pedicle, infected tumors in an otherwise normal uterus, similar types of fibroid associated with pregnancy, aberrant fibroids, pedunculated submucous fibroids in and beyond the cervix, and fibroids of the cervix. The postoperative course in the ordinary types of uterine fibroids removed by myomectomy varies with the location, size, and number of the tumors and the presence or absence of endocervical or occasional endometrial infection. Hemorrhage and infection are the two common sources of morbidity and mortality.

In the selection of the 73 women who were treated with radium in this series, the generally accepted contraindications to radium were taken into consideration.

These include:

1. Size. Radium is contraindicated for fibroids larger than the size of a twelve- to fourteen-week pregnancy.

2. Position. Subserous or pedunculated submucous fibroids.

3. Tumors producing pressure or pain symptoms.

4. Tumors undergoing degeneration or infection.

5. Rapidly growing tumors.

6. Tumors associated with inflammatory pelvic disease, postoperative adhesions, or other newgrowths such as endometriosis.

7. Stenosis of the cervix.

8. Severe bleeding or marked anemia.

9. Pregnancy.

10. Retrodisplacement.

11. Age. The severity of the symptoms of the postradiation menopause is in direct relation to the prematurity of the induced menopause. Thirty-five years was the original arbitrary age limit under which radium was contraindicated. General experience has raised this level to forty years. In this series 24.3 per cent of women were still menstruating at the age of forty-six. For this reason it seems desirable to consider radium, if at all, only in the fifth decade and as close to the expected menopause as can be determined.

12. It is further to be noted that radium is contraindicated after the menopause is established.

13. Radiophobia.

The decreased frequency (2.1 per cent) in the selection of radium as a treatment for fibroids in 1933 as compared with the percentage (15.0 per cent) in 1923 is not entirely explainable by the presence

of the usual contraindications to radium.   There is much literature
on the unfavorable results following the use of radium.   Norris[17] re-
ports 8 per cent failures; Schmitz,[21] 12 per cent; Ford,[6] 31 per cent;
and Keene,[11] 6.5 per cent.   In this series dosage ranged from 800 to
2,800 mg. hr.   Eight women required a second application of radium,
one of these requiring subsequent hysterectomy, a total incidence of
11.11 per cent failure.   The average interval between the first and sec-
ond irradiation was eleven months.   The dosage in the failure group
ranged from 1,200 to 1,800 mg. hr.   In this series there were no known
cases of carcinoma of the corpus.

In general the statement may be made for the gynecologic depart-
ment of Michael Reese Hospital that radium in the treatment of fibroids
is no longer a primary choice in patients in whom the usual contra-
indications are not found; rather its selection is limited to those pa-
tients in whom any type of operative removal is contraindicated.   If
radium is ill adapted to these latter patients, then roentgen ray therapy
is utilized.   It should be borne in mind that this attitude has reference
only to patients with fibroids and not to those who have a simple
fibrosis uteri.

There were 7 deaths in this series, a mortality of 0.7 per cent.   Among
the last 484 patients there was one death, or 0.21 per cent.   The causes
of death were pulmonary embolism in 2, cerebral embolism in one,
peritonitis in 3, streptococcus infection in 2, and Welch's bacillus in one,
and intestinal obstruction in one.   Of these 7 patients, 5 had supra-
vaginal hysterectomies, and 2, myomectomies; the mortality for myomec-
tomy was 1.64 per cent while by contrast the mortality among 791 pa-
tients in whom every type of hysterectomy was done was only 0.63
per cent.

DEATHS

CASE 1.—Mrs. J. S., white, aged forty-one years, married, gravida iv, para 0,
supravaginal hysterectomy performed for fibroid $13 \times 8 \times 6$ cm.   She died on fourth
day of peritonitis and ileus.   W.B.C., 13,600; temperature, 103° F.; pulse, 150.

Postmortem findings: generalized fibrinopurulent peritonitis.

B. Welchii recovered from cultures.

CASE 2.—Mrs. G. E., white, twenty-seven years old, married one year, gravida 0.
Myomectomy for two fibroids 3×3.5 cm., and appendectomy.   Wound infection
fourth day.   Definite peritonitis sixth day.   W.B.C., 20,000; temperature, 105.4° F.;
pulse, 120.   She died on eighth day.   No postmortem.

CASE 3.—Mrs. E. B., white, aged forty-nine years, married, gravida iii, para i.
Supravaginal hysterectomy for fist-sized fibroid plus left inguinal herniotomy.   Pulse
over 112 from second day.   Temperature, 100 to 102° F.   Evisceration on eighth
day.   Wound resutured after loop of adherent bowel freed.   Temperature 105° F. for
three days.   Died on eleventh day.

Postmortem findings: diffuse purulent streptoperitonitis, subdiaphragmatic ab-
scess, gangrene of loop of small bowel.

CASE 4.—M. R., aged twenty-seven years, single, gravida 0. Myomectomy for fibroids 4 cm. and 8 cm. in diameter; considerable oozing at time of operation; distention and ileus marked by fourth day; obstructive symptoms fourth day. Reoperation on sixth day showed hematoma of right cornu with kinked and adherent ileum; bowel freed and ileostomy done. W.B.C., 8,000; temperature, 105.2° F.; pulse, 150. Died eighth day.

Diagnosis: peritonitis following intestinal obstruction. No postmortem.

CASE 5.—Mrs. J. R., white, aged forty-eight years, married, gravida v, para iii, supravaginal hysterectomy and bilateral salpingo-oophoritis for multiple fibroids. On sixth day temperature, 102° F.; pulse, 88; pain in chest plus râles plus decreased resonance plus bronchial breathing. Diagnosis: early bronchopneumonia. Two attacks of dyspnea plus cyanosis on fourteenth day and she was placed in an oxygen tent. Temperature, 103.4° F.; pulse, 104; x-ray picture of chest, negative on fifteenth day. Sudden attack of dyspnea and cyanosis followed by death on eighteenth day.

Postmortem findings: thrombosis of left pudendal vein. Multiple large emboli of right auricle. Old and new emboli of pulmonary artery. Pulmonary infection.

CASE 6.—S. G., forty-six years old, white, single, had mitral stenosis, multiple large fibroids, mass $24 \times 19 \times 12$ cm. Supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed. Auricular fibrillation on second day. Ninth day, pain in right leg and ecchymosis. Gangrene of right foot on twentieth day. Hemiplegia on twenty-sixth day. Sudden death from cerebral embolism on forty-second day. No postmortem.

CASE 7.—Mrs. N. B., white, aged forty years, married, gravida iii, para iii. Supravaginal hysterectomy performed for multiple fibroids and repair of ventral hernia and perineorrhaphy made. Febrile course from right thrombophlebitis of right leg. Sudden chest pain plus cyanosis and dyspnea on sixteenth day. Patient died in fifteen minutes of pulmonary embolism. No postmortem.

The noteworthy postoperative complications in this series included 21 abdominal wound infections (2.5 per cent). Peritonitis occurred 4 times with 3 fatalities. There were 7 instances of evisceration with 6 recoveries and 2 instances of resuture for separation without infection or evisceration. Intestinal obstruction was observed in 3 patients with one fatality. There were 14 instances of thrombophlebitis and 3 of embolism.

TABLE XIV. POSTOPERATIVE COMPLICATIONS

	MORBIDITY	MORTALITY
Wound infections	19	(2)
Peritonitis	1	3
Eviscerations	6	1
Wound resuture—no infection	2	
Intestinal obstruction	2	(1)
Thrombophlebitis	14	(1)
Embolism		3
Febrile 10 + days	7	
Pneumonia	6	
Shock	5	
Cardiac	4	
Hemorrhage	2	
Psychosis	2	
Anterior tibial nerve paralysis	1	
Rectovaginal fistula	1	
Total	72—7.2%	7 deaths—0.7%

Seven patients had fever of undetermined origin for over one week. Six patients developed a postoperative pneumonia with recovery. Postoperative shock occurred in 5 patients. There were 4 patients who developed cardiac complications; 2 had a decompensation; one an auricular fibrillation; and one an acute exacerbation of a preexisting endocarditis. There were 2 instances of postoperative hemorrhage with recovery. There were 2 postoperative psychoses and one anterior tibial nerve paralysis. Rectovaginal fistula developed once following a vaginal hysterectomy and colpoperineorrhaphy.

SUMMARY AND CONCLUSIONS

The case records of 1,001 patients treated for fibroids of the uterus during the past eleven years at the Michael Reese Hospital are analyzed.

No evidence was found to justify the conclusion that fibroids result from ovarian pathology.

Absolute sterility in this series was apparently due to tubal pathology and not to the presence of fibroids or ovarian pathology. Of the 1,001 patients 73.5 per cent had one or more children; 80.4 per cent either had offspring or had aborted, leaving an absolute sterility of only 19.6 per cent.

Pelvic malignancy was found in 0.9 per cent, there being 5 sarcomas in fibroids and 4 carcinomas of the corpus uteri.

The frequency of total hysterectomy shows an increase from 1.4 per cent in 1923 to 14.6 per cent in 1933. Vaginal hysterectomy shows a steady increase from 5.5 per cent to 18.1 per cent. Supravaginal hysterectomy remains the most frequently used treatment for fibroids, 56.2 per cent in 1923 as compared with 57.6 per cent in 1933. Myomectomy has its own group of indications. In the younger age group where there are one or more children, it is being supplanted by supravaginal hysterectomy, 21.9 per cent in 1923, 7.6 per cent in 1933.

The selection of radium as the treatment for fibroids has steadily diminished because of the increasingly long list of direct contraindications, the undesirability of a precipitate menopause, the inability to examine the pelvic and abdominal viscera and an appreciable percentage of failures, 11.1 per cent. Radium was used in 15.0 per cent of cases in 1923 and 2.1 per cent in 1933.

Partial or complete removal of the adnexa was performed in 47.1 per cent of the patients. Indications for these operations on the adnexa included not only pathology, but mechanical reasons and prophylaxis.

The total mortality in this series was 0.7 per cent (7 deaths). In the last group of 484 consecutive patients there was one death (0.21 per cent).

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BLOOD CHEMISTRY IN PREECLAMPSIA AND ECLAMPSIA*

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THE etiology of eclampsia still remains one of the major obstetric problems awaiting solution.   It has mystified all investigators up to the present time and will perhaps continue to do so until the science of chemistry finally unlocks the secret.   The advance of medicine does not depend so much on spectacular discoveries as on the process of adding knowledge, stone upon stone.   The gradual accumulation of accurate data, obtained through painstaking and laborious investigations carried out by a host of workers throughout the world, will ultimately reveal the cause of this "disease of theories."   Such has been the history of most of the outstanding discoveries in medicine.

This study presents our findings for certain blood constituents in 108 eclamptic and 40 preeclamptic patients.   As we regard preeclampsia to be the same disease entity as eclampsia, we are reporting in one paper the values on the total 148 patients.   The blood components under discussion are the nonprotein and urea nitrogen, uric acid, chlorides, sugar,

alkali reserve, thioneine, and glutathione.   We are not reporting here the values for inorganic elements, acid-base equilibrium, inorganic acids, blood moisture, and lipoids, as these have been previously reported.[1, 2, 3, 4]

METHODS

We have used whole blood in the determinations for nonprotein nitrogen, urea nitrogen, uric acid, sugar and chlorides. As soon as the blood was obtained from the patient, a Folin-Wu filtrate was made and analyses carried out immediately. The nonprotein nitrogen was determined by the Folin-Wu method; the blood urea nitrogen, by the Van Slyke-Cullen modification of the Marshall method, as well as by the Van Slyke-Plazen method in the last 50 patients; uric acid, according to Folin's method, the chlorides, by the Whitehorn procedure, the blood sugar, by the 1928 and, in the more recent analyses, by the 1931 method of Benedict; and the CO_2-combining power, according to the technic of Van Slyke. All values are expressed in milligrams per 100 c.c. of blood, except the CO_2-combining power, which is recorded in volumes per cent.

For the determination of glutathione we have used the method of Benedict and Gottschall.   At present there is no entirely satisfactory procedure for the determination of thioneine.   To obtain a blood filtrate which contains all of the thioneine present in blood, one must use tungstomolybdic acid, described by Benedict and Newton, as a precipitant.   Benedict has suggested a method for the estimation of uric acid, in which the thioneine is removed from the blood filtrate by acid lithium chloride and silver nitrate.   The thioneine is carried down with the silver chloride thus formed.   Utilizing this procedure, one may obtain the value for thioneine, expressed in terms of uric acid, by carrying out a uric acid analysis on the blood filtrate before and after the separation of uric acid and thioneine.   The difference obtained, multiplied by 7.5, gives the actual thioneine value.   As a check, one may redissolve the silver chloride in sodium cyanide and perform a uric acid analysis, which will give the thioneine in terms of uric acid.

RESULTS

Our results are based on the analysis of 692 blood samples.   Due to this large number of determinations it is not feasible to record all findings on each patient studied.   For this reason we present in Table II those in 10 consecutive preeclamptic patients.

Although in most patients frequent blood samples were obtained, these tables show only two sets of values; in eclampsia, those for two specimens, one taken at the height of the convulsive period and the other after complete recovery from the disease, while in preeclampsia, the one was taken immediately before delivery and the other after recovery.   We feel that these two sets of values are more comparable and instructive and less confusing.   Later in the paper we present in certain patients values obtained throughout the course of the disease.

In Table III are given the average findings in the total 148 patients, eclamptic and preeclamptic.   These again do not represent the averages of all the determinations.   The average values for each eclamptic patient during the convulsive and recovery periods, respectively, form the basis for the total average figures for all patients.

In order that the average values in blood uric acid and sugar may be properly evaluated we have prepared Table IV, which gives the maximum and minimum values for fifty consecutive eclamptic patients.

TABLE I.   20 CONSECUTIVE ECLAMPTIC PATIENTS

CASE NO.	DURING CONVULSIVE PERIOD						AFTER RECOVERY					
	N.P.N.	U.N.	URIC ACID	SUGAR	CHLO-RIDES	CO_2	N.P.N.	U.N.	URIC ACID	SUGAR	CHLO-RIDES	CO_2
1	42.6	18.8	6.1	126	466	40.0	27.9	8.4	3.5	77	447	45.7
2	30.8	10.7	4.7	90	531	49.4	35.7		3.2	81	485	52.7
3	39.4	10.7	5.4	61	485	45.7	34.3	10.4	4.0	73	467	52.0
4	34.7	14.0	4.9		471	45.3	34.9	16.3	3.7		493	44.9
5	54.6	16.3	8.0			46.8	40.0	21.5	4.0	189		48.1
6	32.6	12.1	5.8		508	43.8	31.6	11.7	3.8		498	48.5
7	30.8	10.7	4.7	90	531	49.4	35.7		3.2	81	485	52.7
8	35.3	13.1	6.7	99	485	50.4	34.7		4.8	70	493	65.5
9	35.5	13.3	6.5	61	488	51.3	29.4		4.7	90	515	53.7
10	37.3	13.2	6.1	90	459	47.0	30.8		2.9	83	465	48.5
11	33.7	13.5	4.8	88	538	41.9	38.7	12.5	2.6	93	488	60.7
12	33.3		5.7		492	32.4	29.7		3.2	79	468	50.9
13	37.0	13.3	8.0	144	472	30.5	30.0		3.5	90	485	56.0
14	34.5	17.7	5.8		500	30.0	33.9	18.2	4.4		478	51 0
15	36.1	9.3	5.6	143		35.7	33.3		3.9	104		56.9
16	32.1		4.9	108	490	36.2	34.9		2.5	77	540	54.1
17	45.8	14.9	8.8	94	512	36.7	31.6		4.0	81	531	44.2
18	40.2		9.6	72	515	39.0	30.0		3.5	90	485	56.0
19	41.6		5.8	86		59.7	44.7		3.1	111		62.6
20	32.1		6.7	105		51.7	36.6		2 9	95		44.3

TABLE II.   10 CONSECUTIVE PREECLAMPTIC PATIENTS

CASE NO.	IMMEDIATELY BEFORE DELIVERY						AFTER RECOVERY					
	N.P.N.	U.N.	URIC ACID	SUGAR	CHLO-RIDES	CO_2	N.P.N.	U.N.	URIC ACID	SUGAR	CHLO-RIDES	CO_2
1	35.7	14.4	4.0	75	498	46.6	33.0	14.7	3.5	79	496	51.3
2	38.7	14.8	5.2	65	478	43.0	34.5	17.4	3.7	79	482	55.1
3	29.7	9.3	5.5	73	490	42.8	39.2	11.2	3.6	81	456	50.0
4	29.1	8.0	4.4	83	429	57.9	26.6	9.0	3.0	78	457	49.0
5	35.1	10.7	4.0	75	508	50.4	37.5	10.0	3.3	93	495	55.6
6	32.6	9.4	4.1	69	450	42.0	33.0	14.7	3.5	79	496	51.3
7	33.1		4.2	71	455	43.0	31.6	10.3	3.8	74	482	50.4
8	31.2	8.2	4.2	63	462	40.5	39.2	11.2	3.6	81	456	50.0
9	30.3		5.3	54	469	50.4	37.5	10.0	3 3	93	495	55.6
10	41.4		5.3	73	501	40.0	28.8		3.1	81	493	54.1

TABLE III.   AVERAGES FOR 108 ECLAMPTIC AND 40 PREECLAMPTIC PATIENTS

CONDITION	N.P.N.	U.N.	U.N. N.P.N.	URIC ACID	SUGAR	CHLO-RIDES	CO_2
Eclampsia—before convulsions	33.1 (20)*	13.4 (8)	0.405	4.2 (18)	70 (17)	508 (11)	43.0 (20)
Eclampsia—during convulsions	38.3 (74)	15.6 (28)	0.408	6.5 (61)	109 (50)	492 (23)	37.4 (70)
Eclampsia—before delivery	36.1 (70)	14.9 (31)	0.413	6.2 (62)	120 (45)	500 (11)	38.1 (71)
Eclampsia—recovered	33.6 (64)	13.6 (20)	0.405	3.5 (64)	81 (12)	483 (21)	52.7 (63)
Preeclampsia—before delivery	31.3 (30)	10.5 (14)	0.336	4.6 (30)	75 (23)	477 (25)	41.1 (29)
Preeclampsia—recovered	34.2 (31)	12.4 (15)	0.363	3.6 (31)	83 (28)	475 (29)	52.6 (30)

*The figures in parentheses represent the number of patients studied.

Table V shows the values for thioneine and glutathione in six cases of eclampsia. The thioneine is expressed in terms of uric acid. In order to obtain the real value for thioneine, the figure in column B or C must be multiplied by 7.5. In columns D and E are expressed the values for uric acid, after correction for thioneine according to either the "indirect" or "direct" thioneine figures. In column F are given the glutathione values.

TABLE IV. BLOOD URIC ACID AND BLOOD SUGAR IN ECLAMPSIA
(MAXIMUM AND MINIMUM VALUES)

CASE NO.	URIC ACID		SUGAR		CASE NO.	URIC ACID		SUGAR	
	MAX.	MIN.	MAX.	MIN.		MAX.	MIN.	MAX.	MIN.
1	4.9	2.5	108	66	26	8.4	3.9	196	95
2	8.8	3.6	95	81	27	5.0	4.0	120	91
3	6.2	2.8	150	77	28	7.2	5.1	76	68
4	6.1	2.9	105	66	29	5.5	5.2	100	50
5	5.4	2.6	93	65	30	5.2	3.2	200	61
6	5.7	3.2	134	66	31	6.8	2.9	125	87
7	11.4	4.0	118	61	32	13.4	6.1	89	71
8	9.6	3.5	144	65	33	6.7	2.8	143	93
9	4.7	3.2	90	81	34	11.4	3.6	83	56
10	6.8	4.8	99	67	35	5.0	3.1	133	67
11	7.6	5.4	104	66	36	5.6	1.8	95	50
12	7.3	4.0	95	61	37	14.4	4.5	100	59
13	5.2	3.3	104	65	38	5.0	3.1	91	71
14	11.4	2.8	98	69	39	4.0	2.5	118	62
15	10.2	4.9	167	63	40	9.4	6.7	167	105
16	9.0	4.0	167	83	41	6.1	3.3	111	77
17	4.4	2.8	88	61	42	5.3	2.9	77	53
18	6.1	3.1	105	78	43	5.3	2.9	118	76
19	7.0	3.8	100	47	44	8.8	4.0	87	56
20	6.7	3.4	100	55	45	4.7	3.6	154	87
21	5.6	2.8	108	68	46	10.0	3.9	167	100
22	6.4	3.1	94	64	47	6.7	2.8	222	62
23	7.6	3.8	109	77	48	8.8	4.0	189	143
24	7.0	4.0	130	74	49	6.3	3.7	113	100
25	10.8	4.9	95	73	50	4.7	4.2	100	80

DISCUSSION

In normal pregnancy at term the nonprotein nitrogen is within the normal nonpregnant range, being approximately 28 mg. per 100 c.c. of blood. In eclampsia and preeclampsia the value remains within this normal range, being 33.1 and 31.3 mg., respectively. The only deviation from the normal is an increase late in eclampsia. It is significant that values obtained at the onset of the disease are all within the normal limits, and it is only as the disease progresses that we find a slight nitrogenous retention, as expressed by the nonprotein nitrogen value. Furthermore, this increase disappears as the patient recovers. These findings show fairly conclusively that should a nitrogenous retention appear in an eclamptic patient, it does so late in the disease and is strongly suggestive evidence that kidney damage plays no rôle in the etiology of the disease. Such retention is undoubtedly caused by the eclamptic "toxin," or agent, on the kidneys. In many of our severely sick

TABLE V. THIONEINE AND GLUTATHIONE IN 6 ECLAMPTIC PATIENTS

CASE	DATE	A URIC ACID DETERMINED	B THIONEINE INDIRECT EXPRESSED AS URIC ACID	C THIONEINE DIRECT EXPRESSED AS URIC ACID	D URIC ACID FROM A & B	E URIC ACID "CORRECTED" FROM A & C	GLUTA-THIONE	DELIVERY	CON-VULSIONS
D.	Sept. 26	8.4	0.0	0.9	8.4	7.5	41.7	Sept. 26	Sept. 26
	Sept. 28	5.2	0.3	0.7	4.9	4.5	29.9		
	Oct. 10	4.2	0.7	0.9	3.5	3.3	35.7		
B.	Oct. 9	7.5		0.4		7.1	33.8	Oct. 9	Oct. 9
	Oct. 10	3.0	0.3	0.3	2.7	2.7	25.3		
	Oct. 11	2.5	0.0	0.3	2.5	2.2	22.7		
W.	Oct. 15 9 A.M.	4.8	0.9	1.3	3.9	3.5	45.8	Oct. 15	
	Oct. 15 10 P.M.	5.6	1.1	1.2	4.5	4.4	47.0		
	Oct. 18	6.9	0.3	0.9	6.6	6.0	41.2		
	Oct. 19	5.8	0.5	0.9	5.3	4.9	40.9		Oct. 19
	Oct. 21	4.9	0.7	1.0	4.2	3.9	32.7		
	Oct. 23	3.7	0.5	0.8	3.2	2.9	33.8		
LaF.	June 17	5.6	0.0		5.6		33.8	June 18	June 17
R.	May 16	7.3	0.0		7.3		37.8	May 12	May 23
K.	Feb. 16 9:40 A.M.	6.1					30.2		Feb. 15-16
	Feb. 16 2:30 P.M.						30.0		
	Feb. 18 9:30 A.M.	6.1					23.0		
	Feb. 18 12:15 P.M.	6.0					24.6		
	Feb. 20	4.2					23.1	Feb. 21	

eclamptic patients, the nonprotein nitrogen remained within normal limits throughout the disease.

The urea nitrogen in eclampsia shows no remarkable change and agrees with the average value for normal pregnancy.

Caldwell and Lyle[5] and Stander[6] found in normal pregnancy a decrease in the urea nitrogen to nonprotein nitrogen ratio. In normal nonpregnant women this ratio, according to Stander, is 0.57 while in normal pregnancy at term the ratio is 0.44. The values reported by Caldwell and Lyle are 0.50 and 0.39, respectively. From Table III it will be noted that in eclampsia and preeclampsia, this ratio is from 0.405 to 0.413 for the former and from 0.336 to 0.363 for the latter.

Marked liver damage, as shown by Mann[7] in dogs and by Rabinowitch[8] and Stander[9] in acute yellow atrophy, results in a definite decrease in urea nitrogen in
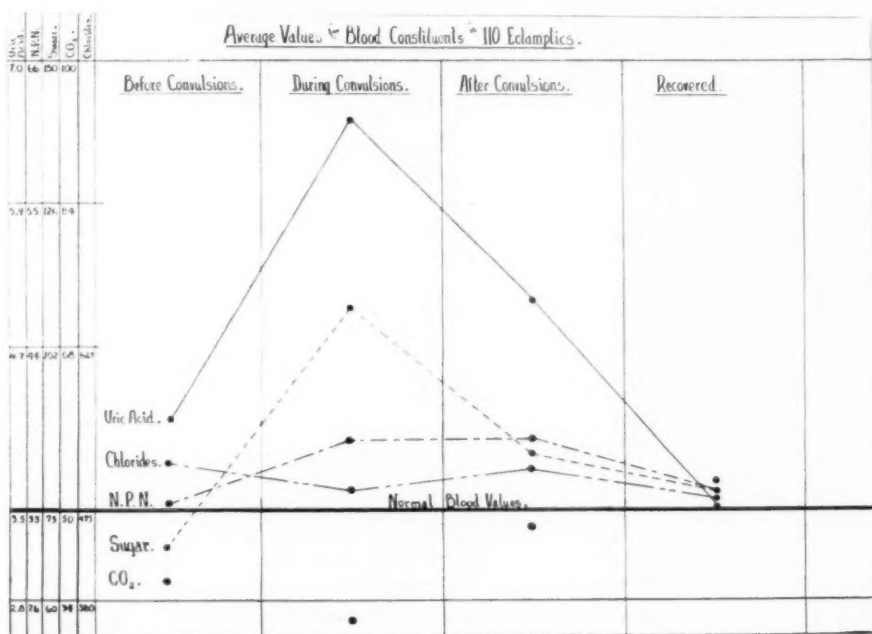
Chart 1.

the blood. The liver destruction in eclampsia is evidently not complete enough to reduce markedly the blood urea nitrogen. A fundamental problem awaiting solution is the cause of the relatively low amount of blood urea nitrogen as is shown clearly by the decrease in the urea nitrogen to nonprotein nitrogen ratio, with a normal nonprotein nitrogen.

Perhaps the most outstanding change in the blood constituents of eclamptic patients is seen in the uric acid. A study of the first four tables as well as Charts 1 and 2 clearly shows this deviation from the normal. The increase in uric acid is out of all proportion with the slight changes in the other nitrogenous constituents and is present before the outbreak of convulsions. Even in the preeclamptic stage we observe a rise in uric acid to 4.6 mg. per 100 c.c. In Chart 1 we have

plotted the average values for the blood constituents on the basis of
the same percentage deviation from the normal, which is indicated by
the horizontal line marked "normal blood values." This demonstrates
graphically the remarkable increase in uric acid values and their return
to normal following recovery. The similarity between the uric acid
changes in eclampsia and preeclampsia is brought out in Chart 2. The
contours of the two curves are almost identical, except that the one for
eclampsia rises above that for preeclampsia during the duration of the
disease. We are unable at present to explain the depression in the
curves shortly before delivery. It may prove of significance as we learn
more about purine metabolism.
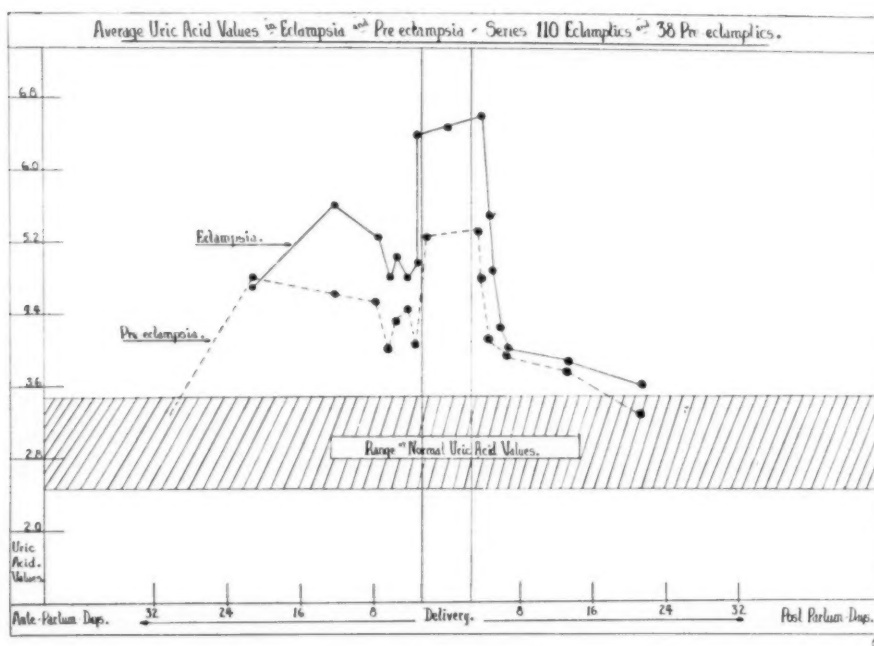
Chart 2.

The question as to the cause of the increased amount of uric acid in
the blood of an eclamptic patient is a very fascinating problem. In
nephritis, uric acid, contrary to the older beliefs, is not the first nitrog-
enous substance to be retained. One may observe normal excretion of
uric acid even in badly damaged kidneys. There appears to be no rela-
tionship between its excretion and that of urea. Quick has shown that
there are certain agents which increase uric acid excretion and others
which decrease it. According to Quick, uric acid excretion may be ac-
celerated by various antiketogenic compounds, such as glycerol, pyruric
acid, glycerin, and alanine and also a high protein diet, while its ex-
cretion can be depressed by ketosis and by lactic acid.

As yet we are not in a position to state that the excretion of uric acid is decreased in eclampsia. There is, however, sufficient evidence to date to make us believe that the accumulation of uric acid in the blood in eclampsia is not the result of decreased kidney function, but rather the result of a metabolic change. This metabolic change seems to be dependent upon liver damage. We know that eclampsia is accompanied by an increase in lactic acid.[10] This increase arises either from a disturbance in the reconversion of lactic acid to glycogen or to an overproduction. One of us[11] has previously stated that a slowing down of the "lactic acid to glycogen" step in carbohydrate metabolism due, let us say, to asphyxia or anoxemia may explain the very marked lactic acid accumulation in eclampsia. That this increase in lactic acid may in turn decrease uric acid excretion seems probable from the work of Quick. However, the experiments of Bollman, Mann, and McGath,[12] on hepatectomized dogs, proved conclusively that the destruction of uric acid depends on the liver and that with liver injury uric acid accumulated in the blood stream even with excessive excretion of this substance by the kidneys. We must bear in mind, however, that uric acid metabolism in the dog and in man may not be the same, and much further investigation is needed before the final work on this metabolism in man may be written. The greater part of uric acid formed and excreted in man seems to originate from oxidized purines, although there is some evidence that endogenous uric acid in slight amounts may be formed from lactic acid and urea. The exogenous uric acid is formed from the hydrolysis of ingested nucleins into free purines, and the oxidation of these to uric acid. Probably from 30 to 70 per cent of uric acid formed, exogenous and endogenous, is destroyed in the liver while from 30 to 70 per cent of uric acid formed in the body is excreted by the kidneys. The destruction of uric acid consists in its oxidation to allantoin with the production of CO_2. It is, however, still a dispute as to what extent man is able to oxidize uric acid to allantoin.

The values for blood sugar, as reported previously,[13] are within the normal range or above the upper limits of normal. After a convulsion a very definite hyperglycemia may appear. In the tables and charts we show the blood sugar at only certain periods during the disease although many more determinations have been performed, some as frequently as every 3 to 5 minutes. Our values to date substantiate our original findings, and we have been unable to observe, except in an occasional case, hypoglycemia. Hypoglycemia follows removal of the liver and may occur if that organ is damaged by disease. Consequently, one would expect hypoglycemia a frequent finding in eclampsia, just as one would expect a diminution in blood urea in this disease. Neither of these blood changes, however, is a constant accompaniment of eclampsia. As stated above, the liver destruction in this disease is evi-

dently not complete enough in the majority of cases to bring about reduction in the blood urea and sugar.

In both eclampsia and preeclampsia the alkali reserve is decreased during the height of the disease. The significance of the decrease in CO_2-combining power we have discussed fully in our earlier communications on the acid-base equilibrium in eclampsia and preeclampsia.

The blood chlorides show very slight changes, except in those patients with marked edema, when a decrease in the chlorides is observed. The values for preeclamptic patients are slightly lower than those in eclampsia. In Chart 3 we present a graphic comparison of the above blood chemical findings in eclampsia and preeclampsia.
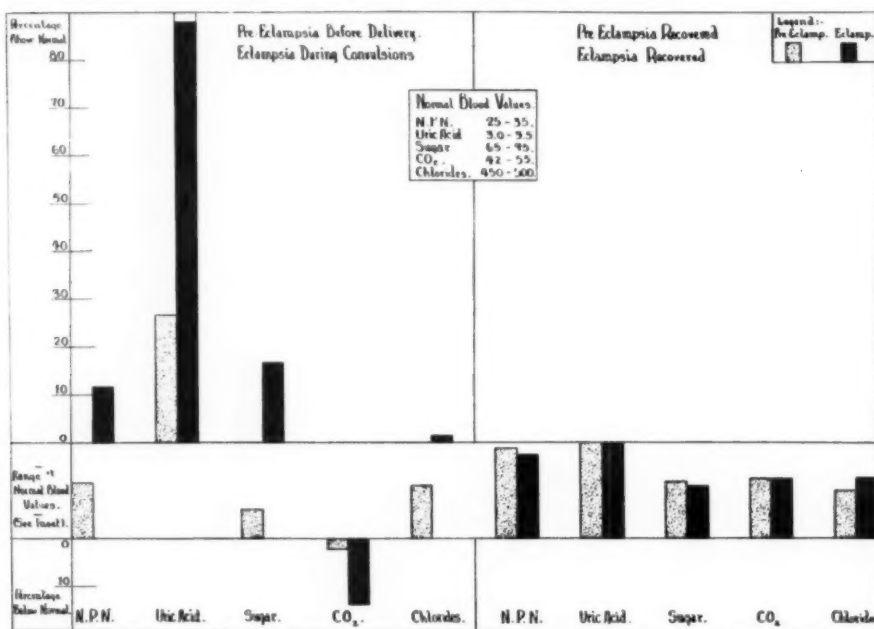
Chart 3.

In order to ascertain if the hyperglycemia, sometimes observed in eclampsia, is caused by the "saccharoid" fraction of the blood, we deemed it advisable to study some of the known nonfermentable copper-reducing substances, present in the blood stream. Benedict proposed the term "saccharoids" to designate the group of nonfermentable copper-reducing materials present in blood. The Folin-Wu method for blood sugar is not specific for glucose as it includes these saccharoids. The saccharoids may be determined by analysis of the blood filtrate before and after fermentation. Benedict, however, has discovered a reagent which eliminates the necessity for fermentation, and gives the true glucose value.[14] Benedict and Newton have reported that both glutathione and thionine are capable of reducing the Folin-Wu copper reagent to the extent of 0.2 of their weight of glucose. Furthermore,

Fashena showed that glutathione accounts for 37 per cent of the reducing power of the saccharoids.[15]   The normal value for glutathione lies between the limits 30 and 48 mg. per 100 c.c. of blood.[16]   From Table V it will be seen that in eclampsia the glutathione value is within these limits.

We have observed a decrease in glutathione during the early puerperium.   This decline in glutathione may be associated with loss of hemoglobin, as Benedict found a parallelism between the percentage of hemoglobin and glutathione content.   The significance is not clear, and we must await further work on this saccharoid fraction.

It will be noted in Table V that the thioneine values obtained by redissolving the silver chlorides are consistently higher than those in the
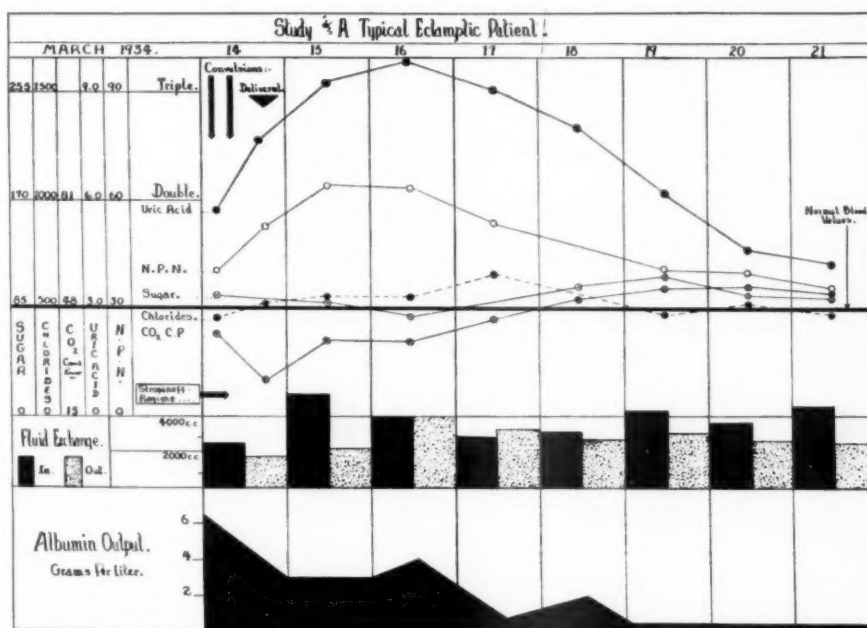
Chart 4.

indirect method.   This is in agreement with the findings of Benedict, Newton, and Behre,[17] who state, ''In many bloods the figures for thioneine by the two different procedures check almost exactly, while in many others the difference between the direct and indirect uric acid values is not as great as the result obtained when thioneine is estimated in the purer form in the silver residue.''   The higher values for thioneine obtained by the separate determination in the silver residue are undoubtedly more accurate.

The value for thioneine in normal blood is between 4.2 and 15 mg. when expressed as thioneine, or 0.56 and 2 mg. when expressed in terms of uric acid.   From Table V it will be noted that in eclampsia the thioneine value lies within this normal range.   From this we may con-

clude that the increase in uric acid, as seen in eclampsia and pre-
eclampsia, cannot be accounted for by an increase in thioneine, but must
be due to an accumulation of uric acid itself. The value of uric acid,
shown in column E of Table V, expresses the corrected uric acid value
and does not differ from the determined value (column A) by more
than it does in normal nonpregnant blood.

In Charts 4 and 5, we present the blood chemical findings in a
typical case of eclampsia. The values are expressed in a manner similar
to that used in Chart 1, which gives the average values for all eclamptic
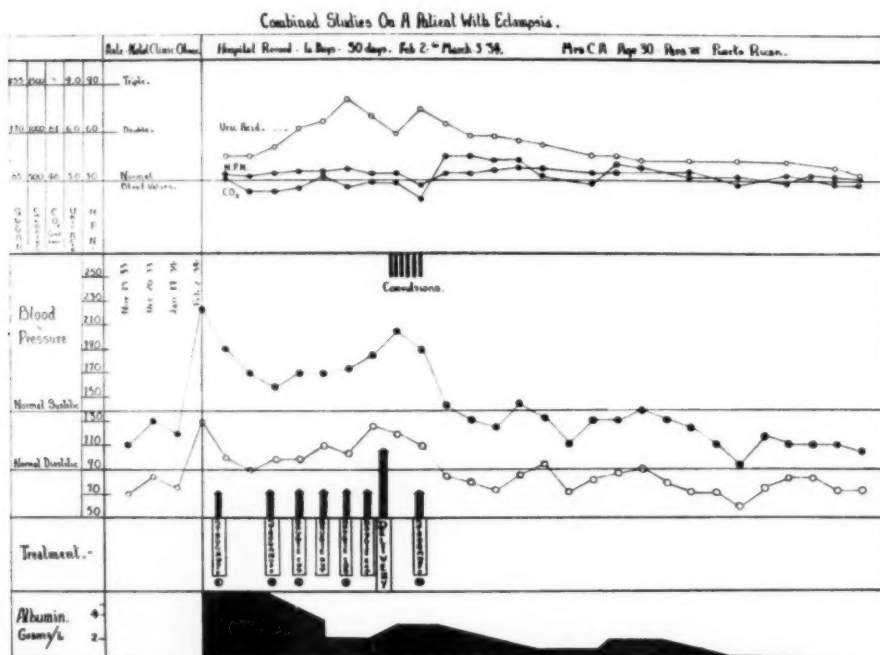
Chart 5.

patients. From these charts it will be noted that the most outstanding
changes occur in the uric acid and CO_2-combining power. It further
demonstrates graphically the complete return to normal. It must be
clear to all that such repeated studies of the blood chemistry gives us an
index of the severity of the disease and often points the way to the type
of treatment necessary. This is especially true in an eclamptic patient
developing true acidosis, and in a preeclamptic patient in whom, in spite
of conservative treatment, the uric acid steadily increases in the blood
stream. This is shown in Chart 6.

We had intended at this time to present our studies on certain frac-
tions of eclamptic blood and their injection into nonpregnant and preg-
nant female rabbits, together with the pathologic and chemical changes
produced. This work, however, has not been completed at the present
time, and we are forced to report it at a later date.

VALUE OF BLOOD CHEMISTRY IN TREATMENT

The chemical findings, presented in a rather condensed form in this paper, are from a sufficiently large number of eclamptic and preeclamptic patients to warrant conclusions as to their *practical* value.   This study has been made over a period of fourteen years and carried out in the Womans Clinics of the Johns Hopkins Hospital and the New York Hospital. One hundred and eight eclamptic and forty preeclamptic patients have been studied throughout their stay in the hospital from a standpoint of their blood chemistry, and the findings correlated with the progress and treatment of the disease. We feel that the blood
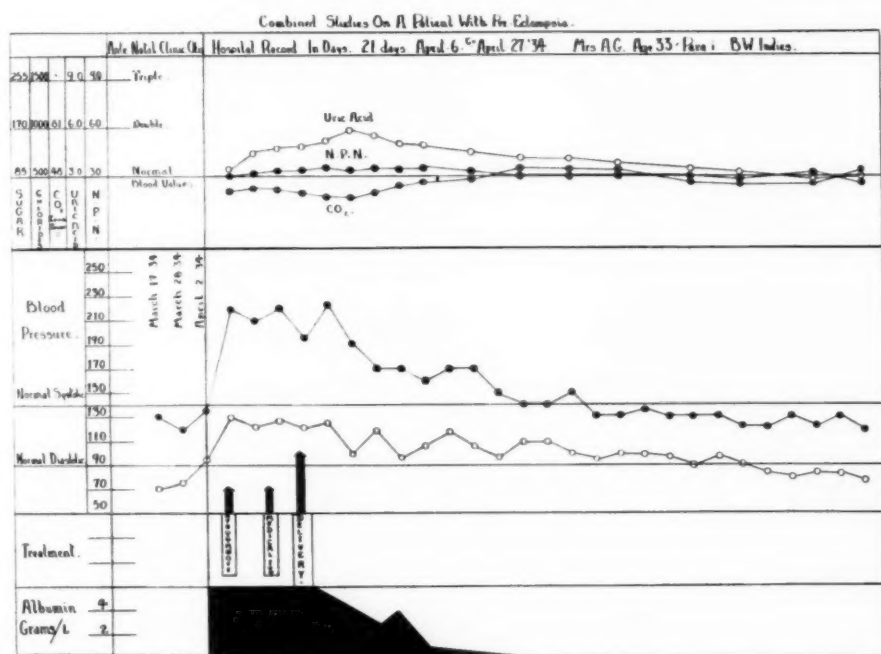
Chart 6.

studies, as indicated in our tables and charts, are as nearly complete as possible, not only so far as any one given blood specimen is concerned, but also as they pertain to the whole duration of and recovery from the disease. During the early years of this work our main purpose was the accumulation of information which may ultimately be used in the elucidation of the etiology of eclampsia. While this is perhaps still uppermost in our minds, we have come to rely, in our treatment of patients, to such an extent on blood chemistry that these studies are routinely carried out in the interests of the patient. Our whole staff, both attending and resident, has come to depend upon the chemical laboratory.

It must be clear, from a casual study of Charts 6 and 7, that the blood chemistry gives us an accurate index of the severity of preeclampsia and the extent of liver damage, if present. We have encountered many preeclamptic patients in whom the degree of hypertension, amount of albuminuria, and presence or absence of symptoms, gave the clinical impression of a mild form, whereas actually the blood chemistry indicated liver damage and impending outbreak of convulsions, as proved by subsequent development. We are fully convinced that careful and routinely repeated examination of the blood for the constituents presented above forms at present our best index of the severity of preeclampsia, and thus is our best criterion for any given type of treatment.

Chart 7.

We have had an unusual opportunity of studying 8 patients, 7 of whom were admitted before the onset of labor and one at the onset of labor, who were diagnosed as preeclamptic and who later developed eclampsia. The chemical findings in all of these 8 patients indicated a steadily progressive aggravation of the disease. A study of the repeated blood chemical analyses, as well as the clinical course, has been convincing evidence to us that preeclampsia is only a stage in the eclamptic disease. Although none of these patients died, we feel that there would have been justification for interruption of the pregnancy in a few in whom this was not done. In a few patients eclampsia developed even after interruption of the pregnancy and delivery of the child either per vaginam or by abdominal section.

As we regard preeclampsia as the same disease as eclampsia, and differing from it only in degree, it is only logical that we should treat preeclampsia as we do eclampsia. Our routine treatment, therefore, consists in first estimating or determining the severity by means of the clinical picture and the blood chemistry. In the mild form of preeclampsia, sedative treatment is usually not indicated, while in the severe form our routine treatment consists in a modified Stroganoff treatment, as used in eclampsia. Should the uric acid content continue to rise, the CO_2-combining power to decrease in spite of treatment, we resort to delivery. The type of delivery will depend upon several factors, such as the patient's past obstetric history, the duration of pregnancy, the status of the cervix and the degree of severity of the disease.

TABLE VI.   TREATMENT IN 58 PATIENTS

TYPE OF TREATMENT AND RESULT	PREECLAMPSIA NUMBER OF PATIENTS	ECLAMPSIA NUMBER OF PATIENTS
Castor oil and quinine induction successful	3	
Castor oil and quinine induction unsuccessful	0	
Castor oil and quinine induction and nasal pituitrin successful	5	
Castor oil and quinine induction and nasal pituitrin unsuccessful	5	
Chloral hydrate only		2
Morphine only	1	2
Insertion of Voorhees' bag and medical induction		1
Insertion of Voorhees' bag and medical induction and Stroganoff		1
Insertion of bougie and medical induction	4	
Insertion of bougie and medical induction and Stroganoff	1	2
Modified Stroganoff treatment	3	5
Modified Stroganoff and medical induction	1	2
Cesarean section	2	
No treatment other than rest and toxemia diet	18	
Total	43	15
Number of mothers died	0	0
Number of babies died	2	2

In cases in which a short easy labor is expected, we favor induction by bougie or bag, otherwise we perform a cesarean section under local or spinal anesthesia. When the outbreak of convulsions is imminent, the sooner delivery is accomplished the better. On the other hand, we do not wish to convey the idea that many preeclamptic patients should be delivered by cesarean section. In 43 consecutive preeclamptic and 15 eclamptic patients admitted to the Woman's Clinic of the New York Hospital since we opened, Sept. 1, 1932, to date, the treatment has been conservative in 96.5 per cent. This is shown in Table VI. From this table it will be seen that in only 2 of 43 preeclamptic patients did we resort to cesarean section. No definite rule can be laid down, as each patient requires individual study, both clinical and chemical, before one

may determine the treatment of choice. We have had no maternal deaths among the preeclamptic patients, and the uncorrected infantile mortality in this group is 4.6 per cent. We should like to point out here that we believe that all fetal deaths, if we are to advance our knowledge from statistical studies, should be reported in the form of total uncorrected "infantile mortality," by which we mean all full-term and premature infants, weighing 1,500 gm. or more, or 35 cm. or more in length, dead-born, stillborn, or dying within fourteen days following birth. Similarly all maternal deaths should be reported in an uncorrected manner.

In the eclamptic group of patients, the blood chemistry assumes even more significance. It gives us not only a true index of the gravity of the disease but points the way to treatment. It is only by such means that one can be cognizant of a developing or true acidosis and of marked liver injury. For the former, immediate antiacidosis treatment is essential; for the latter, glucose therapy is our only rational weapon today. Our treatment for eclampsia, as detailed in earlier publications, is intimately linked up and virtually depends upon repeated blood chemistry studies. We have had occasion to observe 2 eclamptic patients, among the 108 reported, in whom the eclampsia appeared to subside so far as convulsions, clinical symptoms, blood pressure, and albuminuria were concerned, but in whom the blood chemistry indicated progressive liver injury. In these, over a period of three days, following the cessation of convulsions, the uric acid rose steadily to 14 and 16 mg. per 100 c.c. of blood, respectively, and the CO_2-combining power in both remained at a level below 30 volumes per cent. The first patient died before we had fully appreciated the significance of these chemical findings. In the second patient proper therapy, glucose, and antiacidosis measures saved her life. We place far more reliance on the blood chemistry than on such criteria of severity as proposed by Eden.

CONCLUSIONS

1. Preeclampsia and eclampsia are regarded as the same disease.

2. Frequently repeated blood chemical studies in 108 eclamptic and 40 preeclamptic patients reported in this paper show that the blood chemistry is an indispensable index of the severity of the disease and of specific treatment needed.

3. The nonprotein nitrogen content of the blood in eclampsia and preeclampsia remains within normal limits, except in certain instances, late in the disease when a rise indicates involvement of the kidneys as a result of the eclamptic disease.

4. The blood urea nitrogen remains low, as in normal pregnancy, with the result that the ratio between urea nitrogen and nonprotein nitrogen is about 0.4, as compared with 0.5 in normal nonpregnant individuals.

5. The blood uric acid is increased in eclampsia and preeclampsia, indicating, we believe, a disturbance in its destruction in the liver. The

uric acid content in the blood may be regarded as a fairly safe criterion of the severity of the disease.

6. The blood sugar in eclampsia and preeclampsia is not greatly disturbed. Occasionally a definite hyperglycemia follows an eclamptic convulsion, due perhaps to muscular activity.

7. The alkali reserve is often greatly decreased in this disease, sometimes even to the level of true acidosis. The CO_2-combining power is our best and most readily available index of the necessity of antiacidosis treatment.

8. The blood chlorides are not markedly decreased, except in an occasional patient with marked edema.

9. Blood thioneine values in eclamptic patients are within normal limits.

10. Glutathione is similarly within normal limits, except in patients with low blood hemoglobin readings.

11. The increase in blood uric acid in eclampsia and preeclampsia cannot be accounted for by an increase in thioneine.

12. The hyperglycemia sometimes observed in the convulsive stage of eclampsia appears to be a true hyperglycemia and not due to glutathione or thioneine.

We are indebted to Dr. Cloyce R. Tew for the preparation of our various charts.

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525 EAST SIXTY-EIGHTH STREET

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During the five-year period from 1928 to 1932 inclusive there were 16,022 deliveries with 92 deaths, 22 of which were due to puerperal infection. Of the latter patients, only three had been seen in the clinic during pregnancy, nine were infected at the time of admission and ten were in labor.

The causes of death were: General peritonitis, 12 cases; simple thrombophlebitis, 3; suppurating thrombophlebitis, 2; septicemia, 3, and septicopyemia, 2 cases.

JAMES M. PIERCE.

THE MANAGEMENT OF CASES OF THE PERSISTENT ACTIVE PHASE OF ADNEXOPERITONITIS*

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ONE of the peculiarities of salpingitis and peritonitis of gonococcal origin is its tendency, under proper management, to subside to a quiescent status. It is not within the scope of this paper to discuss the mechanisms of immunity by which such quiescence is brought about, or to consider the question of reinfection or of the relighting of quiescent infection. It must suffice to say that quiescence is manifested: clinically, by the subsidence of toxemia, fever, pain, and edema; pathologically, by halting of the progress of the inflammatory damage, disappearance of hyperemia and cellular infiltration, and, later, regressive changes in the newly formed inflammatory tissue, terminating in some cases in virtually complete restoration to histologic and functional normality; and bacteriologically, by a marked diminution in the immediate virulence of the gonococci and other infecting organisms toward their host: that is, by a temporary reduction in their capacity for multiplication and pathogenic activity in the individual patient concerned.

It has been demonstrated by many investigators, and accepted by most clinicians, that laparotomies performed during this quiescent stage carry a much lower mortality and serious morbidity than those done during the active phase. Supplementing an earlier investigation of this question, the data obtained from a study of the records of the Gynecologic Service of the John Sealy Hospital are shown in the table below. In order to obtain a sufficient number of operations performed during the active phase for comparison with the results of operations performed under the present-day policy of deferring operation (if operation becomes necessary) until the quiescent stage is established, two groups of patients operated upon for adnexoperitonitis primarily of gonococcal origin were selected (Table I).

With regard to the data presented above, several important factors must be taken into consideration in applying them to the whole question of the management of gonococcal adnexoperitonitis:

1. This material does not in the least resemble the type of cases encountered in private practice: it is drawn almost wholly from a charity service, nearly all of the patients being of an unintelligent type, incapable of cooperation or of the carrying out of instructions for nonoperative treatment. More than half of them are negroes, from whom absolutely nothing in the way of rest, home treatments, sexual abstinence, or any other cooperation can be expected; in these negroes relighting

TABLE I. COMBINED DATA FROM TWO GROUPS OF CASES

Group 1: 1,000 consecutive cases from a period in which operations were performed without attention to evidences of the activity of the infection. Group 2: the last 2,000 consecutive cases operated upon prior to 1934, in which period an effort has been made to enforce the service rule of avoidance of laparotomy during the active phase of the infection.

	CASES			MORBIDITIES PER CENT				MORTALITIES PER CENT	
	GROUP 1	GROUP 2	TOTAL	NONE	SLIGHT	SEVERE	CRITICAL	INFLAMMATORY CAUSES	NONINFLAMMATORY
Laparotomies for removal of affected structures:									
Without fever on or after admission	417	987	1404	77.04	16.88	4.05	0.86	0.50	0.64
With fever at time of operation:									
99 to 99.9°	193	254[1]	447	40.29	31.26	16.10	9.39	2.01	0.45
100 to 100.9°	77	55[2]	132	33.33	25.00	20.45	14.40	6.06	0.76
Over 101°	43	24[2]	67	26.86	8.95	25.38	25.38	11.94	1.49
Total with fever	313	333	646	37.46	28.02	17.95	12.23	3.87	0.62
With fever on admission, but without fever at time of operation for:									
One day	92	85[2]	177	50.85	29.94	11.86	5.09	1.13	1.13
Two days	59	68[2]	127	55.10	25.20	11.02	4.72	3.15	0.00
Three days	32	335	367	64.48	26.23	6.28	2.19	0.00	0.82
Operations for the drainage of collections of pus without removal of affected structures:									
Posterior colpotomies	52	153	205						
Anterior colpotomies	3	20	23	53.94	16.66	16.66	11.84	0.00	0.88
Drainage of pus by laparotomy:									
Previously unaffected peritoneum exposed to infection	25	2	27	11.11	7.41	11.11	33.33	33.33	3.70
Not exposed to infection	7	17	24	50.00	12.50	33.33	0.00	0.00	4.16

[1]The significance of temperatures between 99° and 99.9° was only recently noted, accounting for the large number of cases in this group; most of these had been admitted with higher temperatures, and were regarded as "cooled" cases.

[2]The incidence of these cases in the second group is due to four factors: (1) Private cases of nonstaff operators not subject to rules of the Service; (2) carelessness of members of Staff; (3) cases of salpingitis complicating a primary condition requiring immediate operation, torsion of pedicles, ectopic pregnancy, intestinal obstruction, etc.; (4) cases of uncertainty as to diagnosis, usually in regard to appendicitis.

of infection and reinfection occur universally, the resulting pathologic damage being incredible to anyone practicing solely among white patients of the higher social levels. Almost the same may be said of the rather large group of Mexican patients. Among the whites, the economic necessity for self-support or for housework almost completely precludes the proper carrying out of the necessarily prolonged ideal schedule for the management of early cases of this type.

2. More than three-fourths of the negro patients present complicating conditions which require operative treatment; more than half of them have fibromyomas of considerable size, averaging about 8 pounds in weight (the largest in this series

weighed 48 pounds, tumors of from 15 to 20 pounds' weight being frequent). Negroes rarely present themselves for treatment until years of recurrence of infection have elapsed: hence the pathologic inflammatory changes present on admission are of the most extreme type in the majority of these cases.

3. In spite of the existence of the conditions just quoted, less than half of the cases of uncomplicated gonococcal adnexitis seen in the Out-Patient Department are admitted to the hospital. Of these, a considerable percentage are treated by non-operative methods and discharged on one or more occasions. Cases of the initial attack of salpingitis are never operated upon; less than one-fourth of the whole number of patients with ''second attacks'' are operated upon. Exceptions to this policy are usually the result of the necessity for operation for complicating conditions or of uncertainty as to the diagnosis between salpingitis and appendicitis or ectopic pregnancy, etc.

This study, therefore, may be considered as the history of an effort: (1) To apply conservative principles to a large group of cases of the maximal pathologic damage wrought by mixed infections engrafted upon adnexoperitonitis primarily of gonococcal origin; (2) to determine principles governing operative intervention in the persistently active and progressive cases, the application of which will result in minimal morbidity and mortality.

The most interesting findings in the first part of this study (which is as a whole merely confirmatory of the findings of other investigators) are as follows:

1. The mortality from infection was less in the group of cases in which the temperature had been below 99° for three days prior to operation than in the group in which no fever was present on or after admission. This may be accounted for by the possibility that many of these latter patients were admitted on the first day, and operated upon the second day, of freedom from fever.

2. The mortality from infection was four times as great in the group of patients operated upon with a temperature between 99° and 99.9° as in the group in which no fever was present on or after admission.

3. The group of cases admitted with high temperatures which subsided rapidly to normal showed lower mortality and serious morbidity rates and less tendency to progress toward suppuration than the group admitted with relatively low temperatures which required a period of several days for subsidence to normal. The latter group showed a higher percentage of abscess-formation, and from our incomplete bacteriologic studies, an universal incidence of cross-infection (usually with streptococci or colon bacilli).

The difficulty in making practical application of the principle of deferring laparotomy until the quiescent status is fully established lies in the determination of a reliable criterion by which the inflammation in the individual case may be adjudged to have reached the state of adequate quiescence and therefore the stage of maximum safety for operation. An early study of our material showed that a number of laboratory proce-

dures, valuable in other types of infection, were not to be relied on for our purposes, as all but one (the sedimentation rate) had a considerable incidence of misleading error. The sedimentation rate was rapid in all active cases; but it remained rapid indefinitely in the presence of massive clot, massive exudate or necrosis (as in complicating fibromyomas). Numerous clinical aspects were studied without result until it was found that the mortality in cases free of temperatures above 99° for seventy-two hours or more prior to operation compared favorably with the mortality in cases free of fever from the time of admission.

It was also found that no additional decrease in mortality was obtained by deferring operation for more than seventy-two hours after subsidence of fever; although the incidence of serious morbidity was slightly lessened. A service rule, which has since proved quite satisfactory, was formulated as follows: Laparotomy is not to be performed in cases of gonococcal adnexoperitonitis until the temperature has been below 99°

Fig. 1.—Sites of incision in 24 laparotomies for the drainage of collections of pus without traversing the previously uninfected peritoneum. In most of these cases the position of the abscess high in the abdomen is the result of elevation of the tubes by large fibromyomas, ovarian cysts, or pregnancy prior to the onset of suppuration.

for at least seventy-two hours and does not rise after a rather vigorous bimanual examination. (This, of course, was simply an attempt to make more definite the general principle previously enunciated by Polak, Miller, and others.) Incidentally, it was found that 400 consecutive cases form a reasonably reliable standard for the study of percentages in cases of this type: in the comparison of units of 100 consecutive similar cases the mortality from inflammatory causes, for instance, varied from 0 to 3 per cent; with units of 200 cases, from 0 to 1.5 per cent; with units of 300 cases, from 0.3 per cent to 1.3 per cent; with units of 400 cases the maximum variation became fractional, and was not materially reduced in the comparison of units of from 500 to 1,000 cases. In units of less than 400 cases a single death causes a disproportionate increase in mortality percentage which is apt to be misleading; but the spread between the 0 per cent in 366 cases and 12 per cent in 67 cases or 33 per cent in 27 cases which occur in our data must be considered as at

least significant. Numerous interesting questions arise in this study, but must be omitted as not being within the scope of this discussion. An exception may be made in regard to the controversial question of drainage: after dividing the material into groups of like cases (febrile cases, cases with massive exudates, cases of soiling with pus, cases of extensive damage to peritoneum or to hollow viscera, cases of continued oozing of serum or of blood from raw surfaces, etc.) it was apparent that serious morbidity was greatly, and mortality definitely, lower for each group in the drained than in the undrained cases; and that the use of folded rubber dam as drainage material was followed by fewer immediate and remote ill-effects than occurred after the use of tubing or gauze. In drainage after laparotomy we have found that bringing the drainage material out through a small stab wound has almost eliminated postoperative hernia and serious infection of the major wound.

The application of the rule quoted above leaves us still confronted with the problem of the management of patients in whom subsidence of fever does not occur under proper treatment; in other words, the management of cases of the persistently active phase of this type of inflammation. The data from our material indicate a serious morbidity in over 30 per cent and a mortality of nearly 5 per cent in 697 cases in which laparotomy was performed in the presence of fever. In most cases sustained fever indicates active suppuration, which is apt to progress and to terminate in hopelessly extensive damage to the genitalia or in death from diffuse peritonitis, sepsis, or exhaustion. Since laparotomy for the removal of affected structures carries an excessive mortality in cases of this type, it becomes necessary to fall back upon the time-honored principle of drainage in order to limit the damage done and to prevent the deaths which otherwise would occur.

There are four methods of approach for the drainage of actual or incipient abscess in the tube, ovary, or peritoneal cavity:

1. The familiar posterior colpotomy, which has been applicable in 205 cases of this series, without mortality from infection.

2. Anterior colpotomy, which is invaluable as an approach to collections of pus lying anterior to the uterus or the broad ligament. In the latter situation the initial finger-dissection should be carried up to the uterovesical fold directly in front of the uterus before the finger is turned laterally between the folds of the broad ligament, in order to minimize the danger of injury to the uterine vessels; injury to the pampiniform plexus has not yet occurred in our material. It is better to enter the pus cavity in these lateral situations from behind, through the anterior fold of the broad ligament, than, having perforated the uterovesical fold in front of the uterus, to enter the pus cavity from the mesial side: since the latter approach may traverse the free peritoneal cavity and lay it open to an exceedingly dangerous infection. Anterior colpotomy has been employed in twenty-three cases of this series, without mortality.

3. The ordinary open laparotomy, in which the previously uncontaminated peritoneal cavity is traversed in the approach and by the drainage tract; and in

this series was followed by a mortality from infection of 33 per cent in 27 cases. We have long since abandoned this procedure.

4. A method of approach by small incisions through the abdominal wall, to areas of suppuration which are inaccessible by either of the vaginal routes; an effort being made to locate the incision over a point at which the parietal peritoneum is adherent to the underlying inflamed structures in order that the previously uncontaminated peritoneum may not be traversed and laid open to infection. This was found possible in fourteen of our twenty-four cases of this type. In four cases the incision entered the free peritoneal cavity; but the area of adhesion to the parietal peritoneum was located by digital exploration, the first incision closed, and a new incision made over a safe point in the adherent area. In six cases no point of adhesion to the parietal peritoneum existed. In four of these an application of the principle employed in colostomy and in the transpleural drainage of subphrenic or hepatic abscess was made: the parietal peritoneum was sutured to appropriate underlying structures and the wound packed with gauze; on the next day the gauze was removed and the abscess opened through the walled-off sinus formed by this procedure. In the other two cases this procedure was not feasible: a circular gauze pack was placed at the most appropriate point, and allowed to remain for three days; withdrawal of the gauze left a walled off tract through which the abscess was perforated. There was no mortality from infection in this small group of cases. The length of the incisions in these operations averaged 1½ inches through the skin (largely dependent upon the thickness of the fat); 1 inch through the fascia or muscle; and only long enough to admit the finger for exploration, through the peritoneum. Longer incisions are apt to defeat the purpose of this technic.

In our earlier work with the four types of operation, their application was limited to cases of frank peritoneal abscess; later, cases of suppurating ovarian cysts were so drained; still later, the principle was extended to the treatment of incipient abscesses (masses of exudate masking the outlines of the pelvic viscera, with areas of softening); and finally, pyosalpinges were opened by perforation with a blunt instrument. Our experience has caused us to extend rather than to curtail the indications upon which these operations are employed. In posterior colpotomy the use of drainage material was found to be unnecessary except in cases where remote lateral pus cavities were drained by way of a long tunnel through exudate or adhesions. In only seven cases was it necessary to reopen the drainage tract. In anterior colpotomy and in the abdominal approach premature closure of the drainage tract is frequent, and drainage material should be employed. As noted above, gauze, cigaret drains, and rubber tubing have all been abandoned in favor of folded rubber dam. In posterior colpotomy, especially, rubber tubing is dangerous as a possible cause of pressure necrosis and perforation of intestine: there were three cases in this series and eight other cases in the records not included in this study. The after treatment of these cases has been reduced practically to rest in bed and observation. If drainage material is used, it is removed at the end of seventy-two hours. A number of years ago injections of milk were made in a fairly large group of cases, but abandoned as productive of considerable dis-

comfort and no apparent beneficial effect. A second series of cases is now receiving this type of therapy as an experimental study.

The final test of the value of a given type of procedure lies in the end-results. Unfortunately, so much of our clinical material is of the irresponsible nomadic type and is drawn from so large an area that we have been unable to obtain a satisfactory follow-up upon the group as a whole. Thirty-two of the colpotomy cases were operated upon for the removal of diseased structures before leaving the hospital, the average interval between the two operations being about three weeks. There was no mortality; but the technical difficulty of the second operation was appalling in the majority, and a few cases had to be abandoned as inoperable. It was gradually borne in on us that the patients who were discharged after refusing a second operation had a better subsequent record than those who were operated upon. As a result, secondary laparotomy before leaving the hospital has practically been abandoned. Of the 243 patients discharged after drainage without secondary operation, nine returned once, one twice, and one three times (after intervals of from three months to fifteen years) for recurrent abscess; seventeen returned for laparotomy, seven of them for unrelated pathologic conditions (in these cases the absence of really troublesome adhesions was notable); three returned pregnant, of whom two were delivered at term. A large number returned to the Out-Patient Department or to other services in the hospital, mostly without serious complaint of pelvic symptomatology (sufficient time for accurate identification and counting of these cases has not been available).

Since this paper is necessarily in the nature of a condensed summary, no conclusions will be drawn except that in almost all cases of the persistently active phase of primarily gonococcal adnexoperitonitis incipient or actual suppuration is present; that in almost all cases drainage of the suppurating areas can be accomplished without contamination of the previously uninvolved peritoneum, through the employment of one of the three types of operation described; and that a material reduction in mortality may be so effected.

UNITED STATES NATIONAL BANK BUILDING

INJURY OF THE URETER IN PELVIC SURGERY

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INJURIES to the lower urinary tract are among the most frequent complications of operative gynecology, with trauma to the ureter more serious than involvement of the urethra and bladder. Considering the great number of pelvic operations performed, ureteral injuries are relatively few. It, therefore, seems timely to present the following 10 cases which have occurred on the Gynecological Service at the University Hospital during the past ten years.

No attempt will be made to review the literature on this subject, but particular attention should be drawn to three classical papers by W. Stoeckel[1, 2, 3] which are ignored in recent American communications. These discussions, including case reports, covered the entire field with such thoroughness that no essential fact has been added in the twenty-five years since they appeared, with the exception of the introduction of pyelography as an aid to diagnosis, and of the technic of ureteral anastomosis by the methods of McArthur[4] and Bump and Crowe.[5] More recent papers discussing various viewpoints and representative of the present opinion include: Schäfer,[6] Furniss,[7] G. v A. Brown,[8] Curtis,[9] Harris,[10] Beach,[11] and Newell.[12]

CASE 1.—S. H. (Hospital No. 66,569), aged forty years, was admitted on Oct. 16, 1924, with carcinoma of the cervix. Radical hysterectomy, including dissection of the ureters, was performed. No ureteral injury was noted during operation. The early convalescence was mildly febrile, and on the fifteenth postoperative day urine began to drain from the vagina, although some was also passed per urethram. Cystoscopy revealed no evidence of vesicovaginal fistula, but the left ureteral orifice was motionless and no urine was seen escaping from it. A catheter could be passed only a short distance on the left side and no urine was obtained. Dye given intramuscularly failed to appear at the left orifice. The patient was discharged on November 17 with leakage of urine still present.

Three months later, the patient reported that the escape of urine had gradually diminished and finally ceased. Unfortunately no further study of the urinary tract was made, and the patient has not been heard from since. This case illustrates the type of lesion which is almost unavoidable in the radical operation for cancer of the cervix, for wide dissection of the ureter, although protecting it from immediate damage, results in interference with its blood supply, or leads to necrosis from pressure of heavy suture material.

CASE 2.—M. M. (Hospital No. B-5423), was first admitted in July, 1927. She was a white multipara, aged twenty-eight years. A diagnosis of laceration of the cervix and perineum, and retroversion was made. Suspension of the uterus was done and

plastic repair of the cervix and perineum was performed. Routine curettage revealed the presence of adenocarcinoma of the corpus. Thirty-five days after the first operation, total abdominal hysterectomy, bilateral salpingectomy, and left oophorectomy were done. The ureters were not exposed, and injury was not suspected at the time of operation. From the second day after operation, large amounts of urine escaped from the vagina, although the patient also voided normally. Cystoscopy revealed no injury to the bladder. Dye injection showed that the right ureter was functioning normally, but that the left was draining into the vault of the vagina. The function of the right kidney was good. The patient was discharged; but returned four months later, when left nephrectomy was performed since the fistula had not yet closed. She was living and well six years later, and showed no recurrence of the malignancy.

CASE 3.—L. K. (Hospital No. D-9290), a multipara, aged thirty-six years, was delivered on the Obstetrical Service on Jan. 3, 1930. On the twentieth postpartum

Fig. 1.   Fig. 2.

Fig. 1.—Case 3 Bilateral pyelogram taken two months after operation, showing mild dilatation of both pelves.

Fig. 2.—Case 3 Bilateral pyelogram taken three years later, showing no increase in hydronephrosis or hydroureter.

day, curettage was performed because of severe bleeding. The curettings showed mucosal cell sarcoma of the uterus. On February 10 total abdominal hysterectomy and bilateral salpingo-oophorectomy were done. In an attempt to remove some of the thickened parametrium without exposing the ureters, a segment of the left ureter was excised and was detected on the specimen immediately after removal. The proximal end of the ureter was located and implanted into the bladder, which was drained constantly with a retention catheter for nine days, after which all urine was passed through the urethra. The urinary output was only 300 c.c. for the twenty-four hours after operation, but rapidly returned to normal.

Cystoscopy fifteen days after operation showed the new orifice functioning normally in the center of a rosette of everted mucosa. The left kidney pelvis was

slightly dilated, and there was a stricture of the right ureter 5 cm. from the orifice with mild hydronephrosis (Fig. 1).

On April 14, 1933, cystoscopy showed the left ureteral orifice as a round punched-out hole from which clear urine spurted. The capacity of the right kidney pelvis was 20 c.c. and of the left 18 c.c. Comparison of the pyelograms shown in Fig. 1 and Fig. 2 indicates that no increase in dilatation of the ureters or kidney pelves had developed in the intervening three years.

CASE 4.—M. L. (Hospital No. F-3511), aged forty-three years, was admitted May 2, 1931, with cystocele, marked erosion of the cervix, and uterine myomas. Myomectomy and left oophorectomy had been performed elsewhere three years previously. Upon celiotomy the bladder was found fixed high on the uterus with the anatomical relations much altered as a result of the earlier operation. In the course of total hysterectomy the left ureter was cut, the stump being found before peritonealization, and implanted into the bladder with moderate tension upon the suture line. A cigaret drain from the region of the implantation was carried out through the abdominal incision. An indwelling catheter provided constant drainage of the bladder.

The convalescence was mildly febrile. Upon the ninth day the abdominal drain was removed and on the tenth the catheter was withdrawn from the bladder. On the thirteenth day urine began to escape from the abdominal incision and the temperature dropped to normal. The drainage stopped in a few days and the patient was discharged in good condition. Cystoscopy showed an area of slough in the region of the implantation but intravenous pyelograms revealed normal kidney pelves and ureters.

Two years later, the patient complained of burning and smarting on urination but otherwise felt well. Cystoscopy showed some distortion of the trigone, but clear urine was seen spurting from the new left orifice. Both ureters were easily catheterized, and pyelograms were obtained proving that no hydronephrosis or hydroureter had developed (Fig. 3).

CASE 5.—E. M. (Hospital No. G-5017), a nullipara, aged forty-six years, was admitted on June 2, 1932. She stated that the appendix and one ovary had been removed eleven years before, and that following this operation an abdominal fecal fistula had drained profusely for eighteen months, but had closed spontaneously. Celiotomy was performed with the diagnosis of myoma of the uterus. Extensive and dense adhesions between the abdominal and pelvic viscera walled off the true pelvis completely, and required a tedious dissection to free the uterus. In addition to a myomatous uterus, large bilateral hydrosalpinges were found. Total hysterectomy and bilateral salpingectomy were done. The right ureter was cut some time during the procedure, and the proximal end, which was found in the wound bed, was implanted into the bladder under considerable tension. An indwelling urethral catheter was left in place for twelve days. The urinary output for the first twenty-four hours after operation was 300 c.c. but rapidly increased in amount during succeeding days. Convalescence was uneventful. Cystoscopy with injection of indigocarmine showed the implanted ureter functioning satisfactorily. Pyelograms were not obtained.

On Sept. 12, 1933, the patient stated that she had passed a bladder stone four weeks previously, but had otherwise been quite well. Cystoscopic examination revealed a right hydronephrosis and hydroureter, the capacity of the right kidney pelvis being 27 c.c. No pus was found and excretion of phenosulphonephthalein was normal. This is the only patient in whom implantation of the ureter into the bladder has been followed by obstruction and pyelectasis. Repeated examinations will be necessary to determine the ultimate fate of the involved kidney, but the prognosis seems doubtful.

CASE 6.—E. S. (Hospital No. G-1655), aged forty-three years, was admitted in March, 1932. In addition to large multinodular uterine myomas, a severe, but readily controlled, diabetes was found. Abdominal total hysterectomy was performed with no difficulty, but after removal of the uterus the left ureter was found to have been cut at a rather high level. It was impossible to bring the proximal end to the bladder for implantation, therefore a simple end-to-end anastomosis was done. After operation, a large catheter was passed up the left ureter through the cystoscope. It seemed to be in the kidney pelvis and was left in place for constant drainage. The total urinary output for the first twenty-four hours was 50 c.c., but increased quite rapidly in amount. However, practically no urine escaped from the ureteral catheter. A high fever developed on the day after operation and continued until the twentieth day. On the tenth day urine began to drain from the vagina, and the leakage was present at the time of discharge on the fortieth day.

The patient was readmitted four months later, and stated that drainage had ceased spontaneously one week previously. Cystoscopy revealed a normal bladder

Fig. 3.   Fig. 4.

Fig. 3.—Case 3 Pyelograms taken two years after operation, showing normal conditions.
Fig. 4.—Case 7 Pyelogram taken nine months after operation, showing normal condition on the injured (left) side.

with a blocked and nonfunctioning left ureter. Intravenous pyelograms showed no shadow on the left side.

This patient illustrates the occasional situation in which ureterovesical implantation is impossible. The procedure of choice here would have been end-to-end anastomosis over a large catheter, with drainage of both upper and lower segments of the ureter through an ureterostomy above the line of repair (Bump and Crowe[5]). An extensive retroperitoneal urinary extravasation evidently developed and finally drained through the vagina. The contraction of the scar tissue about the fistulous opening led to autonephrectomy, which in view of the patient's severe diabetic condition and the desire to avoid further operation, may be considered as a satisfactory result.

CASE 7.—S. B. (Hospital No. G-6347), a white multipara, aged forty-five years, who was admitted in July, 1932, stated that a myomectomy had been performed four

years before in another clinic. Pelvic examination revealed a large cervical myoma filling the true pelvis. Abdominal total hysterectomy was performed with extreme difficulty because of the location of the tumor and the distortion of the anatomical relationships due to dense adhesions resulting from the previous operation. After removal of the uterus, the left ureter was found to have been cut about one inch from the bladder. The distal end was hanging free in the pelvis, and the proximal end was located by dissection along the posterior leaf of the broad ligament. Implantation into the bladder was easily done. Continuous drainage of the bladder was carried out for ten days through a retention catheter. The urinary output was normal in amount from the time of operation. On the eighteenth day, cystoscopy with intravenous injection of indigocarmine showed that the left (implanted) ureter was functioning, and the patient was discharged.

Nine months later, the patient was readmitted. Blood had been seen in the urine on one occasion several months previously and there had been some aching in the right lumbar region and in the right lower quadrant. Cystoscopy showed some puckering of the bladder mucosa around the new left orifice, which appeared as a round punched-out opening, writhing with each spurt of clear urine. There was no obstruction to the passage of ureteral catheters and no residual urine was found in the kidney pelves. The pyelograms, shown in Fig. 4, reveal no evidence of dilatation of the pelves or ureters.

CASE 8.—G. K. (Hospital No. H-2678), aged thirty-nine, was admitted on March 15, 1933, with complaint of irregular vaginal bleeding. An early epidermoid carcinoma of the cervix was found, and radical hysterectomy (Wertheim) was done, no complication being noted during the procedure. The convalescence was uneventful and the patient left the hospital in good condition on the tenth day. At this time there was a residual urine of approximately 150 c.c. The patient returned to the clinic on June 13, 1933, stating that urine began to drain from the vagina a few days after discharge. Examination revealed a small fistula in the apex of the vagina. On cystoscopic examination, the left ureter showed rhythmic contractions, while the right ureter was motionless, and indigocarmine did not appear from its orifice after intravenous injection. Intravenous pyelograms showed a marked hydronephrosis and hydroureter on the right side with a mild dilatation on the left side as well. No treatment was given at this time.

On August 3, 1933, the same findings were noted. An exploratory laparotomy was therefore done. There were many adhesions in the pelvis and the right ureter was found dilated to the size of the index finger. Implantation of the ureter into the bladder was considered not feasible, and nephrectomy was performed. The patient was discharged after an uneventful convalescence.

CASE 9.—M. D. (Hospital No. H-7314), aged sixty-two years, was admitted July 12, 1933, complaining of postmenopausal bleeding. The provisional diagnosis of carcinoma of the corpus was confirmed by curettage. A Wertheim radical hysterectomy was performed, and the left ureter was accidentally cut about one inch from the bladder. An end-to-end anastomosis was done. Urinary drainage from the vagina began on the third postoperative day. A few days later the vaginal mucous membrane sloughed, and the condition became steadily worse until exitus on the twenty-first day. Death possibly resulted from kidney complications as blood chemistry two days before death showed: urea nitrogen 52.5, uric acid 6.3, and creatinine 1.2 mg. per cent. Autopsy was not permitted.

CASE 10.—L. H., aged thirty-eight years (Hospital No. C-3018), was admitted Jan. 3, 1934, with a diagnosis of ovarian cyst, the tumor reaching almost to the umbilicus. The body of the uterus, the tubes, and the right ovary had been removed

in 1926, and a small ovarian cyst had been palpated on the left side in 1928. At operation, Jan. 6, 1934, a large thin-walled serous cystadenoma was found adherent to the left pelvic wall, with the pedicle close to the cervical stump. The left ureter, which was closely adherent to the posterior portion of the pedicle, was accidentally severed about two inches (5.0 cm.) from the bladder. The distal end was ligated and the proximal end was implanted into the bladder 1.5 cm. from the normal ureteral orifice. A retention catheter was introduced into the bladder and left in situ for nine days. Convalescence was complicated by fever which persisted for one month, but for which no adequate explanation could be offered. Cystoscopic examination on January 22 showed a moderately severe cystitis, with the implanted ureter secreting urine normally. It was impossible to pass a ureteral catheter into the left ureter because of its abnormal position. The indigocarmine functional test was good on both sides. Intravenous pyelography revealed the left ureter and kidney pelvis quite normal. The patient was discharged on Feb. 10, 1934, thirty-five days after operation in good condition, the temperature having gradually returned to normal.

DISCUSSION

Injury to the ureter, rarely observed in present-day obstetrics, is an ever present threat in a number of gynecologic operations, especially abdominal total hysterectomy. In this series, the injury occurred six times in the course of ordinary total hysterectomy, and in three others it was associated with the radical Wertheim operation, while in one it developed in the course of extirpation of a large ovarian cyst in a patient who had previously had a hysterectomy. Most often, direct trauma, such as cutting (complete or incomplete), puncture, crushing, or ligation is responsible, but occasionally the wide dissection of the Wertheim technic leads to sloughing of the ureteral wall due to disturbance in its blood supply. This seems to have been the sequence in Cases 1 and 8 of this series.

Conditions which render total hysterectomy more difficult, and which increase the danger to the ureter are: residua of severe pelvic infections, particularly infiltration and shortening of the broad ligaments; intraligamentous and cervical myomata; and distortion of the anatomical relationships by previous pelvic operations. In four of the six cases of ordinary total hysterectomy, in which the accident ensued, one or more of these factors was present. Cases 5 and 7 emphasize the possible bad effects of myomectomy. Each of these women was more than forty years of age when the myoma was removed, and had had several children. After unindicated myomectomies (hysterectomy would have been better) these women were left with the possibility of recurrent tumors, and with abnormal anatomical relations which led directly to serious accidents during the second operations.

The diagnosis of ureteral injury can often be made during the operation, especially by careful inspection of the wound bed before peritonealization, it was thus detected in seven of our ten cases. Escape of urine from the vagina or the abdominal incision, or complaint of incon-

tinence following pelvic operations should always suggest the possibility of ureteral fistula, and should be investigated by cystoscopy when the patient's condition permits. Since postoperative anuria means bilateral ligation of the ureters, until proved otherwise, the diagnosis should be confirmed by immediate cystoscopy with attempts at ureteral catheterization.

Theoretically, this accident should be entirely preventable; in practice, however, it cannot be completely eliminated. This is particularly true when there are congenital anomalies of the ureter, or when the ureter passes directly through tumor tissue. If the anatomy of the cervix and its neighboring structures is normal, the ureter lies 1.5 cm. from the uterus at the level of the internal os, and 1.0 cm. from the cervix at the vaginal reflection. These distances are increased when the bladder is dissected off the anterior wall of the uterus and retracted downward and forward, while upward traction is made on the uterus. Therefore, if the dissection and retraction are properly done, and clamps or sutures are placed as close as possible to the uterus, the safety of the ureter can be guaranteed. In the presence of complicating conditions, the most effective protection for the ureter lies in its exposure throughout its course through the parametrium. No attempt to remove parametrial tissue should be made until this precaution has been observed. Neglect of this rule led to severance of the ureter in Case 3.

The introduction of ureteral catheters preliminary to total hysterectomy may be of great value and has enjoyed extensive use. Stoeckel pointed out, however, that it is occasionally impossible to locate the ureter by palpation even with the catheter in situ, and we have had this embarrassing experience on one occasion. In most cases, it is superfluous, and, as it is not entirely free from danger, should not be employed as routine (Latzko and Schiffmann[14]).

Prevention of ureteral injury during vaginal hysterectomy depends: first, upon proper selection of cases, with elimination particularly of intraligamentous fibroids; second, upon making strong downward traction on the cervix while the bladder is dissected off the anterior wall of the uterus and by subsequent retraction of the bladder anteriorly; and third, by placing parametrial sutures as close as possible to the uterus. By observing these precautions, the ureter has not been injured in any of a rather large series of vaginal hysterectomies performed upon this service.

During the removal of intraligamentous cysts, the ureter may be safeguarded by the use of blunt dissection of the tumor from its bed; in no case should adherent strands of tissue be cut until their nature has been determined. With fibroids developing within the cervix, danger may be avoided by splitting the uterus from the fundus downward and enucleating the tumor, after which the parametria may be clamped and cut close to the collapsed capsule.

A wide variety of procedures is available for the repair of an injured ureter, and proper selection depends upon the type and location of the lesion, the time of discovery, and the general condition of the patient. When complete section of the ureter is discovered before closing the abdomen, the most successful repair consists in implantation of the proximal end into the bladder. This was done five times in this series, with primary healing in all, and in only one has the appearance of an increasing hydronephrosis made the ultimate outcome doubtful. Vesical implantation may, however, be impossible in high injuries which prevent approximation of the stump and the bladder. In such a situation, end-to-end anastomosis over a large catheter appears most promising, but should always be accompanied by drainage of the kidney pelvis through a pyelostomy or ureterostomy above the line of repair. (Bump and Crowe,[5] and Iselin.[15]) Cases 6 and 9 of this series illustrate the poor results obtained by anastomosis without this prophylactic drainage. Should the condition of the patient be so alarming as to prohibit attempts to repair the damage, the proximal end may simply be doubled upon itself and secured with a nonabsorbable ligature, or it may be carried out through the incision or into the vagina, thus creating a fistula to be treated later.

Incomplete section of the ureter may be repaired by simply closing the defect, providing that no more than one-third of the wall is involved. If the damage is more extensive, the section should be completed and the proximal end implanted into the bladder (Latzko and Schiffmann[14]). Bilateral ligation should be treated by immediate laparotomy with removal of the ligatures, if the patient's general condition will permit. Otherwise, bilateral pyelostomy must be performed (Caulk[16]) with the hope that the ureters may be restored when operation can be tolerated.

Postoperative ureterovaginal fistula should be treated expectantly for a time, since spontaneous healing occurs occasionally. If drainage continues for more than six weeks, one should attempt to conserve kidney function by transperitoneal implantation of the ureter into the bladder, which is generally preferable to nephrectomy.

SUMMARY

Ten cases of unilateral injury to the ureter are reported, 6 of which were incidental to ordinary abdominal total hysterectomy, while three resulted from the radical Wertheim hysterectomy, and one from removal of an ovarian cyst. The accident occurs during such operations because of complicating anatomical distortion, resulting from previous pelvic operations, residual pelvic inflammatory disease, or cervical tumors. In 7 cases the diagnosis was made during operation, while in the remaining 3 the postoperative appearance of a ureteral fistula was the first sign. Two of this latter group were probably due to secondary sloughing of

the ureteral wall following the wide dissection of the Wertheim technic. In 5 women, the damage was repaired by immediate ureterovesical anastomosis with primary healing in all and with a satisfactory end-result in 4, since hydronephrosis of mild degree has developed in the fifth. In two instances, end-to-end anastomosis was attempted with failures in both; death following in one and loss of the kidney by autonephrectomy in the other. Among the 3, which were undiagnosed at the time but which developed fistulas, one healed spontaneously possibly by autonephrectomy, and nephrectomy was necessary in the other two after healing had failed.

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PROFESSIONAL BUILDING

Lennér, A.: Determinations of Citric Acid and the Occurrence of Citric Acid in Human Tissues, Acta Obst. et Gynec. Scandinav. 14: Supplement 1, 1934.

The author believes there must be a relation between temporary melena neonatorum and the citric-acid content of the mother's blood and that the advantage of the addition of citrate in blood transfusions is not purely technical. The chief bases for this assumption are, (1) the clinical observation of a better effect from the use of 2 c.c. of a 10 per cent sodium citrate solution than from the same amount of a 2 per cent solution in sinus transfusions of citrated blood from mother to newborn child in cases of temporary melena neonatorum and, (2) the fact that the onset of melena in children coincides with a marked increase in the citric-acid content of the mother's milk.

The citric-acid content of the serum seems to be only slightly decreased in pregnant women, beginning in the third month of gestation.

Immediately before the onset of labor there is a considerable increase in the serum citric acid of the mother. This persists or rises slightly during labor and the first postpartum hours. After six hours this value falls reaching a minimum on the fourth day at the latest. This minimum persists up to and including the eleventh day. From then on there is a gradual rise and about three weeks or one month after delivery the figure characteristic for the nonpregnant woman is reached. The retroplacental blood is rich in citric acid. There possibly exists a certain relation between the amount of hemorrhage with the afterbirth and the citric-acid content of the mother's blood.

There is a ten- to twenty-fold increase in the citric-acid content of the mother's milk on the second, third, or fourth postpartum days.

J. P. GREENHILL.

ANALYSIS OF ERRORS INHERENT IN PREGNANCY TESTS BASED ON THE ASCHHEIM-ZONDEK REACTION*

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THE rapid and widespread application of the Aschheim-Zondek reaction to pregnancy diagnosis has led to the accumulation of a large amount of data collected under both clinical and experimental laboratory conditions. Early workers reported an accuracy of 98 to 99 per cent for pregnancy tests based on the presence of gonadotropic substance in urine. For some time after publication of the details of the Aschheim-Zondek mouse test and those of the Friedman rabbit test, much of the work in this field was of the nature of experimental clinical investigation. Reports were based on experience with small numbers of cases among which there were few problems in differential diagnosis. Not many abnormal pregnancies were studied. The nonpregnancies investigated consisted largely of normal males and females and hospital convalescents, not necessarily gynecological patients. False positives were obtained in such relatively rare conditions as hydatidiform mole, chorionepithelioma, and some cases of uterine carcinoma. Wilson and Corner[1] reported one case of endometrial hyperplasia which gave a false positive by their rabbit ovulation test. Occasionally, negative results, obtained very early in pregnancy, were found to be followed by positive tests shortly afterward.

An increasing number of reports appearing during the past two years have dealt with the use of these tests as routine laboratory procedures. The data represent experience with several hundred cases per series. Few late pregnancies are included except such as present abnormalities. The nonpregnant groups are comprised almost entirely of gynecologic problem cases. Mazer and Hoffman[2] presented an analysis of results of pregnancy tests in 314 problem cases. In this series the accuracy of the Aschheim-Zondek mouse test proved to be considerably less than that reported by other investigators. The incidence of error was 21 per cent of the total number of cases. The negative tests were 90 per cent correct, while only 73 per cent of the pregnancies were correctly diagnosed. Ziserman,[3] in a recent paper, offered a table summarizing the results obtained in 356 problem cases tested by a modification of the Friedman rabbit test. This method gave correct results in 94 per cent of these cases. The percentage accuracy was practically the same in the pregnant as in the nonpregnant group. In contrast to these and other reports, Sondern and Silverman,[4] in applying the original Aschheim-Zondek and the Friedman methods, both as individual and as concurrent tests, to 1,048 cases, recorded that inaccuracies occurred as incorrect negatives only. Positive results in 6 hydatidiform mole cases were listed as correct. The absence of false positives in this

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large series may be due, as suggested by the investigators, to the system of diagnosis employed.   However, it is not improbable that such results are attributable to the fact that there were few problem cases in the group analyzed.   More than 70 per cent of the total number of cases were classed as normal pregnancies.

Uniform accuracy in different laboratories, or even in the same laboratory at different times, is scarcely to be expected since the incidence of error is governed not only by the total number of tests made but also by the proportion of problem cases in the series under consideration. For a short time after the Wisconsin General Hospital offered pregnancy diagnosis as a routine laboratory service to the physicians throughout the state, general interest in the test itself prompted the sending of specimens from apparently normal pregnancies for test at this laboratory.   Soon, however, the nature of the requests for service changed. The specimens received now are chiefly from cases presenting problems in diagnosis.   Those from normal pregnancies are largely from cases in which a very early diagnosis is desired.

The experience of this laboratory now includes more than 800 tests by one or more methods utilizing the Aschheim-Zondek principle.   The accuracy of the laboratory diagnosis has been checked by the subsequent clinical course in 425 cases.   Approximately one-fourth of these were tested by both an immature rat test and by a modification of the Friedman method.   The technical details of these two procedures, as used in this laboratory, have been given in another communication.[5] The rabbit ovulation test only was used in the remaining cases, with an immature female rabbit test as a confirmatory measure in a few instances.   The latter differs from the Schneider method[6] in that dual, rather than single, injection technic is used and in that ovary inspection at operation, rather than at autopsy, permits the use of one animal for 3 tests.

Table I presents a general summary of this series of 425 tests.   It may be seen that the total accuracy was slightly more than 90 per cent. Errors occurred both as incorrect negatives and as false positives, with a predominance of the latter.   Analysis of the data of Table II, which lists the various conditions encountered among these cases, reveals that more than 72 per cent of the series offered problems in diagnosis.   Faulty technic accounts for less than 2 per cent of the erroneous diagnoses. All other discrepancies, 8 per cent of the total series, probably represent systematic errors due to limitations inherent in pregnancy tests by these methods.   Many of the incorrect results, particularly among the false positives, can be correlated with known gynecologic problems in which there was demonstrable endocrine disturbance.

The results of a detailed study of the discrepancies of this series, which it is the purpose of this paper to report, serve to give a clearer

TABLE I

A. Analysis of all tests:		
Total number of tests followed	425	(100.00%)
Correct diagnoses	385	(90.59%)
Positives	217	(51.06%)
Negatives	168	(39.53%)
Incorrect diagnoses	40	(9.41%)
Incorrectly negative	12	(2.82%)
Incorrectly positive	28	(6.59%)
B. Analysis of tests in pregnant cases:		
Total number of pregnant cases	229	(100.00%)
Correctly positive	217	(94.76%)
Incorrectly negative	12	(5.24%)
C. Analysis of tests in nonpregnant cases:		
Total number of nonpregnant cases	196	(100.00%)
Correctly negative	168	(85.20%)
Incorrectly positive	28	(14.80%)

TABLE II.   PREGNANT GROUP

Total number of pregnancy cases	229	(100.00%)
Test correctly positive	217	(94.76%)
Normal pregnancies	99	(43.23%)
Duration of 3 weeks or less	35	
Duration of 4 to 12 weeks	53	
Social cases	11	
Problem cases	118	(51.53%)
Ectopic	6	
Early abortion	11	
Incomplete abortion	8	
Cystic ovaries complicating pregnancy	5	
Fibroid uterus complicating pregnancy	6	
History of irregular menses	23	
Menses in early months of gestation	6	
Intermittent bleeding	18	
Amenorrhea (?) of beginning menopause	11	
Obesity with amenorrhea	8	
Sterility of 7 to 10 years	4	
Fetal heart tones not audible	3	
Lactation	4	
Intrauterine pregnancy and pelvic abscess	1	
Intrauterine pregnancy and appendicitis	2	
Delayed delivery (macerated fetus in one case)	2	
Test incorrectly negative	12	(5.24%)
Systematic errors	9	(3.92%)
Duration less than 2 weeks (positive later)	2	
No known pathology (negative at 3 months)	1	
Abortion at 4 months (negative at 10 weeks)	1	
Uniplacental twins (one mummified, fibroid uterus)	1	
Infarcted placenta (6 months' macerated fetus)	1	
Pernicious vomiting with acidosis (positive later)	1	
Menses during early pregnancy (infection)	1	
Probable attempted abortion (history unreliable)	1	
Technical errors	3	(1.31%)
Inadequate amount of urine injected	2	
Formalin preserved specimen	1	

conception of the significance of such errors and also suggest a means of reducing the frequency of their occurrence. These findings also indicate that, with adequate knowledge of the case history, the individual and species differences characteristic for the various modifications of the Aschheim-Zondek reaction may be utilized as a diagnostic and a prognostic aid in cases of hormonal imbalance in both pregnant and nonpregnant individuals.

PREGNANT GROUP (ANALYSIS OF INCORRECT NEGATIVES)

In this series a correct laboratory diagnosis was obtained in approximately 95 per cent of the 229 pregnancies (Table II) of which 55 per cent were cases presenting diagnostic problems and 16 per cent were cases of pregnancy of less than three weeks' duration. Although in the majority of pregnancies, there is little need for certainty of diagnosis as early as the third week, in a comparatively small but important group, the establishment of the diagnosis at this early date is a distinct advantage. Among the urines from 37 pregnancies of this stage, there were but 2 which failed to give positive results by at least one of the 3 methods used in this laboratory. In one of these cases, the test urine was obtained one week after impregnation. Neither the mature rabbit nor the immature female rats responded to the injection of this specimen. A markedly positive reaction, by both of these methods, followed the injection of a specimen obtained ten days later. The immature rabbit test applied to this second specimen of urine was negative. Another case was found to be negative at two weeks and positive at four weeks. The immature rabbit test was not used on either specimen from this case since the results of the rat and the mature rabbit tests were in agreement. In many of the early pregnancies of this series, the immature rabbit test has been negative when one or both of the other tests were positive. This has been interpreted as indicating that the female rabbit, at from sixteen to eighteen weeks of age, is not sufficiently sensitive as a test animal for the detection of the small quantity of gonad-stimulating substance present in many of the urines of early pregnancy. In this laboratory the immature female rat test has been found more consistently accurate as a supplementary or confirmatory test in cases of very early pregnancy.

Little emphasis has been placed on either the occurrence or the significance of incorrect negatives in pregnancies of more than one month in duration. Wiesner[s] reported premature termination of pregnancy in 7 of 22 cases in which a negative Aschheim-Zondek reaction was obtained, although later observations showed that a pregnancy existed at the time of the test. Since he also encountered several cases which terminated in normal deliveries, although the tests did not become positive until the fourth or sixth month, he concluded that in many cases in which the gonadotropic content of the urine is low, pregnancy ends in abortion while in others it reaches full term. Wiesner has called attention to the fact that this reaction may be negative in the presence of a degenerating placenta, in which condition the production of the gonad-stimulating principle may have ceased.

In this series the majority of systematic errors, as listed in Table II, occurred in pregnancies of more than one month's duration. All but one of these were associated with gestational anomalies of some type. At approximately the third month of gestation, the urine from one patient gave a negative Friedman test. The negative report was based on the fact that there were no ovulation points in the ovaries of the test animal. The excessive ovarian stimulation, indicated by the presence of hemorrhagic corpora, could not be further investigated, since there was not enough of the specimen to permit running other tests, as is usually done in such

cases. The results of the one test were given as a tentative report, pending the receipt of a requested second specimen of sufficient amount to allow testing by more than one method. This specimen was not sent. No details of the clinical course of the case were obtained other than that the pregnancy proceeded to term. This may have been a case analagous to those reported by Wiesner in which the gonad-stimulating substance was absent in the early part of gestation. It is quite probable, however, that this negative test is referable to animal variation and that the error would have been corrected by repetition of the test or by concurrent use of other methods. It is now the policy of the laboratory to withhold the report, under such circumstances, until the receipt of a second specimen makes possible the corroboration or refutation of the original findings. The biologic diagnosis finally rendered is based on the results of 2 agreeing tests.

In this group one case, which terminated in abortion, gave a negative test at the tenth week and a positive test at the fourteenth week of gestation. We are indebted to Dr. J. C. Doolittle of Lancaster, Wisconsin, for the following case history:

The patient reported menstrual irregularity of several years' standing. After a ten-week period of amenorrhea, during which time 4 doses of theelin were administered, a urine specimen was found negative for pregnancy by both the rabbit ovulation and the immature female rat tests. These 2 methods gave positive results on a urine obtained four weeks later. Two weeks after the positive returns were given, spontaneous abortion of a four-month fetus occurred.

In spite of the fact that the tests were correctly positive at the fourteenth week, the absence of a demonstrable quantity of gonad-stimulating substance in the urine ten weeks after fertilization, coupled with ultimate abortion, indicates hormonal imbalance throughout this pregnancy. It is possible that a pituitary or ovarian disturbance was responsible for both the abnormal gestation and for the menstrual irregularity which antedated it.

The presence of a normal and an abnormal fetus arouses particular interest in the negative results obtained at the sixth month of pregnancy in a case referred by Dr. G. C. Waufle of Janesville, Wisconsin:

At a laparotomy performed in April, the fibroid uterus appeared to be gravid. A urine specimen obtained one month later was reported as negative for pregnancy. In August the patient delivered uniplacental twins, one living and one mummified.

It is a matter of speculation as to whether the abnormal fetus exerted some inhibitory influence on the production of gonad-stimulating substance usually found in the presence of a living fetus, or whether the fetal pathology and the absence of active principle in the urine were of the same etiology.

Another instance of low hormone concentration in the urine of a six-months' pregnancy came under observation at the Out-Patient Department and in the Wisconsin General Hospital. Negative tests were obtained at approximately the second and the fourth months. Two months after the last test the patient entered the hospital and spontaneously delivered a six-months' macerated fetus. The placenta was almost completely infarcted. A test specimen obtained eight hours after delivery elicited no response in either mature rabbit or immature rat ovaries. Failure to obtain a positive pregnancy test at the second month is probably evidence that infarction had begun at that time, although it apparently did not interfere with the development of the fetus for some time. It may be seen by reference to Table II that, in one case among those testing correctly positive, the excretion of an appreciable amount of hormone continued in the presence of a macerated fetus which was retained beyond the estimated date of delivery. In the latter case the placenta was apparently normal.

In a recent preliminary report, Smith and Smith[9] have presented data which correlate the toxemias of late pregnancy with an excessive amount of gonadotropic substance in the blood and urine. One experience of this laboratory suggests that a similar study might be of value in early pregnancy cases of hyperemesis with acidosis. This patient entered the hospital complaining of excessive daily vomiting, dating from the cessation of a very brief menstrual flow six weeks before. The emesis did not respond to treatment and the patient was acidotic at the time the urine was sent for the pregnancy test. The ovaries of the mature rabbit and those of the immature rats were not visibly affected by the injection of this urine. The vomiting slowly responded to medication and after an interval of ten days, when the patient was no longer acidotic, positive tests were obtained by both the mature rabbit and the immature female rat methods. Further study of other cases of hyperemesis or of nausea in early pregnancy may reveal a relation between the excretory level of gonadotropic hormone and these conditions. It would also be of interest to investigate the effect of acidosis in itself on the secretion of the active principle.

One case of this series gave a negative test at approximately the third month of gestation and yet the pregnancy terminated with the delivery of a full-term infant. Through the courtesy of Dr. John Tasche, of Sheboygan, Wisconsin, we are able to present the details of the course of this pregnancy.

Seven weeks after the last menstrual period, the uterus of this patient was found to be the size of a three- or four-months' pregnancy. Hydatidiform mole was suspected. At this time a urine specimen, sent to the University of Wisconsin pregnancy diagnosis service, was reported negative by the rabbit ovulation test for pregnancy. Three months later a positive Aschheim-Zondek mouse test (laboratory of Dr. Tasche) was obtained. In the interval between these 2 tests a Lane plate, about which there was a mild infection and absorption, was removed from the tibia. The patient went into labor one month before the expected time and delivered a living full-term child. There was moderate polyhydramnion throughout this pregnancy.

Since the time of conception as indicated by the date of delivery, and the cessation of menses do not correspond, it is apparent that this was a case of bleeding in early pregnancy. The low hormone content of the urine may have been associated with the pathology of which the bleeding was another symptom. It is also possible that the positive pregnancy test at the fourth month of gestation and the normal termination of the pregnancy are evidences of an adjustment of the hormone balance as a result of the healing of the infection after the removal of the tibial plate. In a previous communication from this laboratory[5] attention was called to the fact that rabbits with staphylococcal infections frequently do not respond to the injection of pregnancy urine until the

lesions have healed. An analagous hormonal disturbance might accompany infection in the pregnant woman.

The accuracy of the laboratory result in one of the 9 cases, listed here as negative systematic errors, might be more correctly recorded as equivocal. It was suspected that an attempt had been made to interfere with a known pregnancy. The negative laboratory test was accepted as confirming this suspicion until, upon her return to the clinic for treatment of uterine infection, the patient reported that a complete abortion had been induced shortly after the specimen was sent in for the pregnancy test. Although there is no definite proof that the products of conception were viable or even present at the time of this reported abortion, this test must be listed as incorrectly negative. It is to be expected that other cases of this type, the details of which never become known, will occur among both the pregnancies and the nonpregnancies of any series. An indeterminate number of the inaccuracies will be due to errors inherent in the system of checking the results rather than errors inherent in the biologic system of diagnosis.

NONPREGNANT GROUP (ANALYSIS OF FALSE POSITIVES)

With the exception of 2 cases of genital carcinoma, this group of 196 nonpregnant women was composed entirely of individuals in whom it was important to establish or exclude the existence of pregnancy. The 8 cases listed in Table III as social cases were normal women, not married. The remaining 186 cases, 94.9 per cent of the nonpregnant subjects, presented one or more symptoms suggesting pregnancy at the time the urine was tested. Reports of the subsequent clinical course proved the laboratory diagnoses correct in but 85.2 per cent of the nonpregnant group.

The 3 technical errors of this group occurred very early in the experience of the laboratory. At that time we considered the induction of corpora hemorrhagica in the ovaries of the mature rabbit by the injected urine as evidence of a positive pregnancy reaction. As previously reported,[5] the urine from several cases of endocrinopathy in the nonpregnant has been found in this laboratory to elicit corpora hemorrhagica formation without causing ovulation in such test animals. Therefore, we now accept definite ovulation as the only diagnostic criterion by which to judge a urine positive for pregnancy by the mature female rabbit test.

The total inaccuracy of approximately 15 per cent of the tests in nonpregnant individuals of this series also includes 25 tests which are classed as systematic errors. Among the latter there are 4 cases, one case of retained placental tissue, one of hydatidiform mole, and 2 of genital carcinoma with metastases. Such pathologies in the nonpregnant were early recognized as representing limitations inherent in pregnancy tests

based on the Aschheim-Zondek reaction. A definitely positive reaction was obtained in one case in which placental tissue was retained for some time after termination of pregnancy complicated with severe nephritis.

In the carcinoma cases of this series, correlation of the laboratory results with the clinical and physical findings served in the one case as confirmation of suspected metastasis and in the other as an index to the efficacy of treatment.

TABLE III. NONPREGNANT GROUP

Total number of nonpregnant cases	196	(100.00%)
Test correctly negative	168	(85.20%)
Complete abortion (?), missed abortion, etc.	13	
Menstrual irregularities	65	
Beginning menopause	35	
Pelvic inflammation	10	
Cystic ovaries	10	
Fibroid uterus and amenorrhea	11	
Pseudocyesis	2	
Social cases	8	
Miscellaneous	14	
Test incorrectly positive	28	(14.80%)
Systematic errors	25	(12.76%)
Retained placental tissue	1	
Uterine carcinoma with metastasis	1	
Ovarian papillary cyst—adenoma	1	
Hydatidiform mole	1	
Cystic ovaries and endometrial hyperplasia	9	
Amenorrhea (2 to 6 months' duration)	3	
Menses never regular	2	
Enlarged nonpregnant uterus (operative note)	1	
Beginning menopause or preclimacteric	2	
Temporary interruption of menstrual rhythm	3	
Morning nausea in lactating woman	1	
Technical errors	3	(2.04%)
Positive diagnosis based on presence of hemorrhagic corpora without ovulation in ovaries of mature rabbit.		

One of these patients was referred to this hospital four months after removal of adenocarcinoma of the fundus of the uterus by supravaginal hysterectomy. At this time a urine specimen, tested by the modified Friedman method, produced many ovulation points in the ovaries of the injected animal. Operation upon this patient disclosed metastatic adenocarcinoma of the cervical stump. In the other malignancy case of this group, in which a diagnosis of papillary cystadenoma was made at laparotomy by Dr. W. T. Lindsay of Madison, Wisconsin, extensive invasion of the peritoneum contraindicated further surgical procedure. After 3 courses of x-ray therapy over a period of six months, the urine was tested for gonadotropic activity. Many ovulation points and innumerable new corpora were noted in the ovaries of the mature rabbit while in those of the immature rabbit, hemorrhagic follicles were the only evidence of stimulation. The results of the routine female rat test were essentially negative for pregnancy. The ovaries of the injected animals possessed many large follicles with lutein borders but were no heavier than were those of normal uninjected controls of the same age and body weight. The ovaries of 3 rats, given twice the usual dose of this urine, 10 c.c., were markedly increased in weight and contained both discrete corpora lutea and blood points.

Investigations of Aschheim,[10] Fels,[11] Ehrhardt,[12] Reeb,[13] and others have demonstrated that the gonad-stimulating substance occurs in much higher concentration in urines from cases of hydatidiform mole than in those of normal pregnancy. It has been stated that the presence of 100,000 to 200,000 mouse units per liter may be considered pathognomonic of mole. Mazer and Goldstein[14] suggest that a positive reaction, obtained upon injecting test animals with a urine which has been diluted 10 to 12 times with water, justifies a diagnosis of this condition. The one case of hydatidiform mole included in this series was tested for pregnancy three weeks and six weeks after the last supposedly normal menstrual period. One month after the second test was reported, the expulsion of several vesicles demonstrated this to be a case of mole. The urine specimens sent in for the pregnancy tests had been saved. Complete twenty-four-hour collections of urine were made on twelve successive days following the definite diagnosis. Aliquots of each of these 14 urines were tested by both the rabbit ovulation method and the immature female rat test. At no time did the gonadotropic activity of the urine exceed that noted in normal pregnancies of three or four months' duration. Negative results were obtained in all tests in which the urine was diluted 10 times. Near the end of the observation period, one specimen which had been diluted with an equal volume of water gave a positive reaction by these 2 methods. The rabbit ovulation test became negative forty-eight hours and the immature rat test seventy-two hours after removal of the mole by curettage.

From the standpoint of the value of these pregnancy test methods in differential diagnosis, the remaining 21 false positives of this series merit special attention. Experience gained through a detailed study of the gonadotropic activity of urines from cases of endocrinopathy in nonpregnant individuals indicates that, with concurrent application of 2 or more of these tests to the urine, the accuracy of the laboratory diagnosis is insured. Obviously it would be impractical to submit every specimen received to several test methods. However, it is feasible to make special adaptations of the laboratory routine to meet the requirements of these problem cases. If the laboratory management of such cases is to be satisfactory, it is essential that the case history accompanying the test specimen be sufficiently detailed to serve as a guide to the selection of tests to be applied and as an aid in the interpretation of the results of individual tests or of a group of tests used concurrently. With such correlation of the clinical data and laboratory management, it seems not improbable that the difference in species response or that of the mature compared with the immature female rabmit may be utilized to distinguish the true pregnancy reaction from that induced by the injection of gonadotropically active urine from cases of endocrine disturbance in the nonpregnant.

As a starting point for determining the indications for a particular test or for the use of a group of tests in the biologic differentiation of pregnancy from conditions simulating pregnancy, the 21 false positives obtained in cases of the latter type in this series were divided roughly into groups which include conditions in which the symptoms manifest

up to the time of the test or the ultimate clinical, surgical, or pathologic report were similar. These data were studied in conjunction with the laboratory observations of the effects of the urine on the ovaries of the test animals used for the laboratory diagnosis in each case. Other cases of similar nature were thereafter submitted to more extensive investigations in which the mature rabbit test, the immature rabbit test, and the immature female rat test were concurrently applied to the same specimen. The nature of the response of these different test animals has been noted and the concentration of the active principle in the urine from the different cases has been investigated. In several instances these 3 tests were repeated at frequent intervals during the menstrual cycle. The results of these later detailed studies will be presented together with the analysis of the false positives obtained in conditions of like nature.

Cystic Ovaries and Endometrial Hyperplasia.—In this group of 9 patients, there were 5 cases in which at operation the ovaries were found to be cystic. The curettage tissue obtained at this time showed mild to extreme endometrial hyperplasia associated with the ovarian pathology. The other 4 cases of this group, in which the diagnosis of endometrial hyperplasia was made, were curetted only, hence less definite data as to size and nature of the ovaries were obtained. The ovaries of 2 of these patients were described, in the physical examination note, as palpable and probably cystic. In all cases of this group, we were able to secure rather detailed history of the clinical course previous to the test. Amenorrhea of 6 weeks or more in duration existed in 7 of the patients. Enlarged uterus with softened cervix was recorded in 4 instances. In 3 patients with pain and tenderness in the region of a pelvic mass, tubal pregnancy was suspected. Periods of prolonged and profuse bleeding, with spotting at irregular intervals, were reported in 3 of the 9 cases.

In these 9 cases, the incorrect laboratory diagnoses were based on the results of tests in which the mature rabbit only was used as the test animal. Both ovulation points and corpora hemorrhagica, in the ovaries of all of these injected rabbits, justified the interpretation of the results as perfectly typical pregnancy reactions. Upon reference to Table III, it may be seen that 10 cases of cystic ovary disease gave correct negative tests. In several of these it is known that, as in the majority of those testing falsely positive, there was an associated endometrial hyperplasia. A study of the case histories reveals that many of the symptoms listed above were noted in these patients also. The data accompanying the test specimen included one or more of these clinical features in 6 of these correctly tested cases. The urines, therefore, were submitted to the more extensive investigation as described in a

preceding paragraph of this discussion. The experience in the following case is illustrative of the findings in this group:

The patient was amenorrheic from December 25 until May 25, at which time there was a moderate flow for five days. Spotting, for one day only, occurred on June 25. When first seen at the clinic, July 27, there had been no further evidence of menstruation. By palpation the softened uterus was found to be the size of a two or three-months' pregnancy. The right ovary was three times normal size. The urine specimen, obtained at this time, gave a definitely positive reaction for pregnancy, judging by the presence of many ovulation points and hemorrhagic corpora in the ovaries of the mature test rabbit. The patient denied the possibility of pregnancy. Another urine, voided August 25, was submitted to test by the 3 methods. In the ovaries of the mature test rabbit, there were many ovulation points and hemorrhagic corpora; the ovaries of the immature rabbit exhibited numerous large and extremely hemorrhagic follicles but no rupture points or corpora lutea; there was no significant increase in the weight of the ovaries of the immature rats but there were several large peripherally luteinized follicles in each ovary. The rat uteri were extremely large and distended with fluid. The vaginal orifices were established and the rats were in estrus at the end of the injection period. A third specimen, tested two weeks later by these 3 methods, produced no detectable response in any of the injected animals. At operation, the right ovary of this patient was found to be the size of a lemon and cystic in nature.

The uterine endometrium at this time was slightly hyperplastic. The negative tests obtained two weeks after demonstration of a positive reaction by the mature rabbit test in this patient probably explains why the test was correctly negative by this method in 4 other cases of cystic ovary in this series although neither menstrual history nor clinical features of these cases were known at the time of the test.

Amenorrhea (from two to six months' duration).—Three cases of this type were found to give a markedly positive reaction by the rabbit ovulation test with the mature rabbit. No other tests were used. Inadequate data as to associated conditions and physical findings, make a satisfactory interpretation of these false positives quite impossible. It is not improbable that the underlying cause of these prolonged amenorrheas was endocrine disturbance resulting in an excess excretion of gonadotropic substance in the urine. The clinical facts that are available suggest that these may have been cases of cystic ovary disease of pituitary origin such as those recently described by Sevringhaus[15] in reporting observations made on 63 women who were studied clinically because of symptoms associated with menstrual irregularities. Quantitative studies of the gonadotropic activity of the urines from some of those patients have been made. Complete twenty-four-hour urine collections were obtained at seven-day intervals over periods of five weeks or longer. It was found that the urine from the same individual might at one time give a reaction which could be interpreted as positive for pregnancy, while at other times the results were negative. It is apparent that in cases of such history, the results of a single test are not reliable. Accuracy of diagnosis necessitates either repeated testing of

the urine or the application of several test methods to the specimen, with the interpretation of the results as a single test. This is emphasized by the findings in the following typical case:

Aliquots of the twenty-four-hour urine, collected on the thirteenth day before the beginning of the menstrual flow, produced no detectable reaction in the ovaries of any of the animals used for the 3 test methods. The urine obtained seven days later produced no reaction in either mature or immature rabbit. The ovaries of the immature rats, were not significantly increased in weight as the result of the injection of 10 c.c. of the test specimen per animal over a period of five days. Several discrete, opaque bodies resembling corpora lutea were observed in each ovary. A portion of the urine collected on the fourth day after cessation of an eight-day menstrual flow, produced 9 hemorrhagic corpora and 2 ovulation points in the ovaries of the mature rabbit. The ovaries of the immature rabbit were markedly hyperemic and possessed very large follicles, some of which were hemorrhagic. The ovaries of the immature rats, injected with 10 c.c. of this urine were somewhat heavier than those of the normal uninjected control animals of the same age and weight range. There were neither distinct follicles nor corpora visible in these ovaries, all of them appearing densely opaque and glisteningly white. The urine, voided on the seventh day after the cessation of the eight-day menstrual flow, was without effect on the ovaries of either the mature or the immature rabbits. There were several large follicles with opaque white borders in the ovaries of the injected immature rats.

Menses Never Regular.—In this series false positives were obtained in 2 such cases although there was no known pathology. However, the absence of any sore of menstrual rhythm suggests hormonal imbalance since the establishment of the menses. No clinical data accompanied the test urines from these cases. Superovulation was observed in the ovaries of the injected mature rabbit in each test, hence positive reports were returned. Similar cases, in which the absence of menstrual rhythm was known, have been tested repeatedly by 2 or more methods. The mature rabbit tests were not positive on all of the specimens but the immature female rabbit tests were invariably negative, although a portion of the same urine specimen may have induced ovulation in the mature rabbit. Upon injection of 5 c.c. amounts of urine as routinely used for the detection of gonadotropic activity in pregnancy urine, the ovaries of immature rats are never appreciably increased in weight although one or more large follicles and opaque bodies resembling corpora lutea may be present. The injection of larger amounts of the test urine or of extracts of the urines may cause marked increase in ovarian weight, although the morphologic changes are seldom analogous to those induced by pregnancy urine. In several instances, roughly assaying the urines from cases of this type has resulted not only in correct reports as to pregnancy but also has yielded information as to the concentration of gonadotropic substance in the urine at different times in the same patient.

Beginning Menopause.—In 1930 Zondek[16] demonstrated that the urine of many women, at the beginning of menopause and after castration,

contains a factor which causes folliculation with little or no luteinization in the ovaries of immature rats. According to Leonard[17] such urines also induce ovulation in a rabbit in heat at the time of the injection. In this laboratory, urines from patients known to be within the age limits of the climacteric, or approaching that age, have been tested by the immature rat test rather than by the rabbit ovulation method. Of the 35 cases of this series, in which menstrual irregularity was reported in persons of menopausal age, only 2 have been incorrectly diagnosed by the biological tests. In these 2 false positives, the clinical history available at the time of the test did not include the age of the patient, hence the mature rabbit test only was applied. No incorrect results have occurred when specimens from patients of this age have been tested with either the immature female rabbit or with immature female rats as test animals.

Temporary Interruption of Menstrual Rhythm.—Markedly positive reactions in both the mature rabbits and the immature female rats followed the injection of urines from 3 patients in whom previously regular menses were delayed from one to three weeks. Although these patients subsequently were reported as nonpregnant, the follow-up reports stating that the menstrual flow occurred a few days, one week, and ten days after the specimen was sent to the laboratory suggests that these supposedly normal menstrual bleedings may have been undetected abortions. In no other cases of menstrual irregularity tested at this laboratory have such typically positive reactions been observed in the ovaries of immature rats.

Morning Nausea in Lactating Woman.—Early pregnancy was considered as the possible cause of a four-week period of morning nausea in a woman nursing a four-month-old child. The injection urine caused definite ovulation in the ovaries of a mature rabbit and was reported as positive for pregnancy. Five months later this patient was not pregnant and was menstruating regularly. Detailed history of the reestablishment of the menses was not obtained. Here again, the first supposedly normal menstrual flow may have been evidence of a spontaneous abortion, or lactation may have had some influence on the hormonal balance. The ovaries of rabbit does, with suckling young, usually possess one or more corpora lutea but no large follicles. Such animals do not readily respond to the injection of pregnancy urine. If the young are removed from the mother, she comes into heat within a few days, the follicles enlarge, and the injection of pregnancy urine rarely fails to induce ovulation.

SUMMARY

In 425 cases tested for pregnancy by methods based on the Aschheim-Zondek reaction, a total accuracy of slightly more than 90 per cent of

the series was attained. Three modifications were employed either as individual methods or as concurrent tests with interpretation of the results as a single test. Analysis of the data reveals that erroneous diagnoses, due to limitations inherent in pregnancy testing by these methods, were made in 8 per cent of the cases.

Such systematic errors occurred in 3.92 per cent of the pregnancies. Two were in very early pregnancies testing correctly positive later. In early pregnancies, more consistently accurate results were obtained by a modification of the Friedman rabbit test or by an immature female rat test than by the Schneider immature rabbit method. Incorrect negatives were obtained in 9 pregnancies of more than one month duration. In 7 of these there was definite fetal or maternal pathology; in one there was no known pathology; and in one the history was not reliable.

Faulty tests obtained in 12.7 per cent of the nonpregnant group may be classed as systematic errors. Many of the cases which gave false positive tests can be correlated with known gynecological problems in which there was demonstrable endocrine disturbance. Each of the cases testing incorrectly positive has been studied from the standpoint of the clinical features manifest before and after the test and with respect to the ovarian picture obtained in the injected animals. Correlation of the laboratory and clinical findings suggests that cases of ovarian dysfunction in the nonpregnant can be differentiated from pregnancy by the concurrent application of 2 or more tests to the urine. In cases of this type, false positives have not occurred with the use of either the Schneider immature rabbit or the immature female rats as test animals. The more highly sensitive Friedman rabbit is of value for the demonstration of gonad-stimulating substance in the urines of nonpregnant individuals.

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SUCCESSFUL TREATMENT OF A CASE OF
POLYNEURITIS OF PREGNANCY

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I T IS our purpose to present another case of polyneuritis of pregnancy treated during pregnancy with a high vitamin B intake. The rareness of the condition seemed to justify its presentation.

A white, married female, aged twenty-nine, entered the Indianapolis City Hospital on May 3, 1933, because of weakness, loss of memory, severe pains in the lower extremities, inability to walk or stand, and loss of weight. She had been perfectly well until the beginning of this (her first) pregnancy. Her last normal menstruation began on about Dec. 5, 1932. The patient's past history and family history were essentially negative. Her weight just previous to becoming pregnant was 162 pounds.

During the first week of January, 1933, she had the ''flu,'' which was followed by increasing fatigability and a persistent cough. Within three weeks the attacks of coughing were followed by vomiting. However, the vomiting soon became more severe and more frequent. She then vomited following the ingestion of any food or water, whenever there was any odor of food, and when she was nervous. She became progressively weaker and began to lose weight. Because of the weakness she remained in bed most of the time following the attack of ''flu.'' About the first of March she became unable to walk unassisted. She stated that her knees would give way and she would become very exhausted if she attempted to walk. At about this time she noticed that she could not remember things as well as previously. On March 17 she entered the Coleman Hospital for treatment of the severe vomiting. The patient came under the care of one of us (G. W. G.) at that time.

She then weighed 141 pounds. The blood pressure was 130/90. The pulse varied between 76 and 120 while in the hospital.

Laboratory Findings.—The red blood cell count was 4.47 million; hemoglobin 14 gm. per 100 c.c.; white blood cell count 10,950; and differential: polymorphonuclears 83 per cent, lymphocytes 8 per cent, large monocytes 4 per cent, metamyelocytes 4 per cent, and band cells 1 per cent. Urine: specific gravity was 1.033, sugar negative, albumin negative, acetone 3-plus, and diacetic acid negative; microscopic examination showed 10-12 pus cells, and no casts, red blood cells, or cylindroids.

While in the Coleman Hospital she received daily saline and glucose injections intravenously, frequent carbohydrate feedings, and continuous Murphy drip of glucose and bicarbonate. Under this treatment the vomiting practically ceased, and the patient was discharged from the hospital on March 28, 1933.

During her stay in the hospital she complained of areas of itching on the legs. Soon after leaving the hospital she noticed numbness in the hands and feet. Pain

and marked tenderness in her lower extremities then developed. She also noticed slight numbness over the abdomen. The pains in the legs were especially severe at night and were made worse by changes in the weather. There was no pain in the hands but they felt stiff and full. There was very little vomiting, but slight nausea persisted. The neurologic symptoms progressed, and she noticed marked wasting of the muscles of the lower extremities and inability to control the lower extremities.

On admission to the Indianapolis City Hospital physical examination revealed a well-developed and well-nourished white female lying flat in bed. She was not cyanotic, dyspneic, or orthopneic, and she did not appear to be acutely ill. However, very slight exertion caused dyspnea and an increase in the pulse rate. The patient's memory for recent events was very poor and she was emotionally unstable. The tongue was pale except for the papillae at the tip which were quite red. The left border of the heart measured 8 cm. from the midsternal line. The heart sounds were of good quality. The heart was quite rapid but regular. A slight blowing systolic murmur could be heard all over the precordium. Blood pressure was 115/72. Pulse rate was 122 per minute. The uterus was enlarged up to two fingers below the umbilicus. The estimated length of the fetus was 12 cm. Fetal movements could be seen and felt and the fetal heart rate was 152. The weight of the patient was 135 pounds.

Neurologic Examination.—Cranial nerves were normal. Upper extremities: biceps and triceps were normal; coordination of the upper extremities was approximately normal; there was slight weakness of the hands, but the strength of the arms seemed about normal. The lower extremities were very weak and the muscles of the thighs and calves were very flabby, but slight pressure over these muscles caused marked pain. There was no definite nerve tenderness. The left leg was more involved than the right, there being almost complete paralysis of the left leg. Coordination of both lower extremities was decreased, the left much more so than the right. The knee jerks and ankle jerks were absent. The plantar reflexes were absent. Position sense was normal. Vibratory sense was present but was slightly decreased over the ankles and tibiae. Light touch and hot and cold sensations were apparently normal.

Laboratory Findings.—The red blood cell count was 3.38 million, hemoglobin 58 per cent, white blood cell count 9,700, and reticulocytes 8.8 per cent. The red blood cells were slightly larger than normal and there was slight achromia present. Gastric analysis after histamine stimulation revealed slightly decreased acid and enzyme concentrations, except in the forty minute sample when the free hydrochloric acid was 75 A.P. and the pepsin 4.33 mg. per c.c. Urines were negative except for occasional pus cells. The stools were negative for occult blood. The blood Wassermann was negative. The basal metabolic rate was plus 7 per cent.

MEDICATION RECEIVED BY THE PATIENT

DATE		MEDICATION
5/ 5/33	to 10/20/33	Cod liver oil, drams 2 o.d.
5/ 5/33	to 7/ 6/33	Vegex (autolyzed yeast preparation), 12 gm. o.d.
5/ 6/33	to 6/ 5/33	Liver Extract, vials 3 per day
6/ 5/33	to 10/20/33	Liver Extract, vials 6 per day
5/17/33	to 6/14/33	Iron and ammonium citrate, 30 gr. t. i. d. a. c.
6/14/33	to 10/20/33	Reduced iron, 10 gr. per day
6/12/33	to 7/ 3/33	Liquid vitamin B_1 concentrate (rice polishings), 3 c.c. o.d. (1 c.c. = 500 units vitamin B_1)
7/ 3/33	to _____	Vitamin B_1 capsules (concentrated extract of rice polishings), capsules 8 per day (1 capsule = 200 units vitamin B_1)
5/25/33	to 7/ 7/33	Weekly intravenous injections (20 c.c.) of Liver Extract derived from 100 gm. of whole liver
7/ 7/33	to _____	Weekly intramuscular injections (6 c.c.) of concentrated liver extract derived from 200 gm. of whole liver

As soon as the patient was started on the above medication and a high vitamin diet there was no advancement in signs or symptoms of the disease. The improvement in the mental condition was one of the first signs noted. The pain at night gradually became less. The pulse, which had fluctuated markedly at first, reaching 130 nearly every day, gradually decreased, as shown by Chart 1. The red blood count and hemoglobin percentage showed slow but definite improvement. The patient did not receive full doses of iron during the pregnancy because the large doses of iron produced nausea and vomiting. The red blood cell count reached 4.23 million and hemoglobin 63.7 per cent on the day before delivery. Chart 1 shows also the response of the blood to the medication.

The improvement in the neurologic signs and symptoms is shown in Table I. The most marked improvement apparently followed the administration of the large doses of vitamin B, (as a concentrated extract of rice polishings). As the neurologic symptoms improved, the muscles of the lower extremities became less flabby and
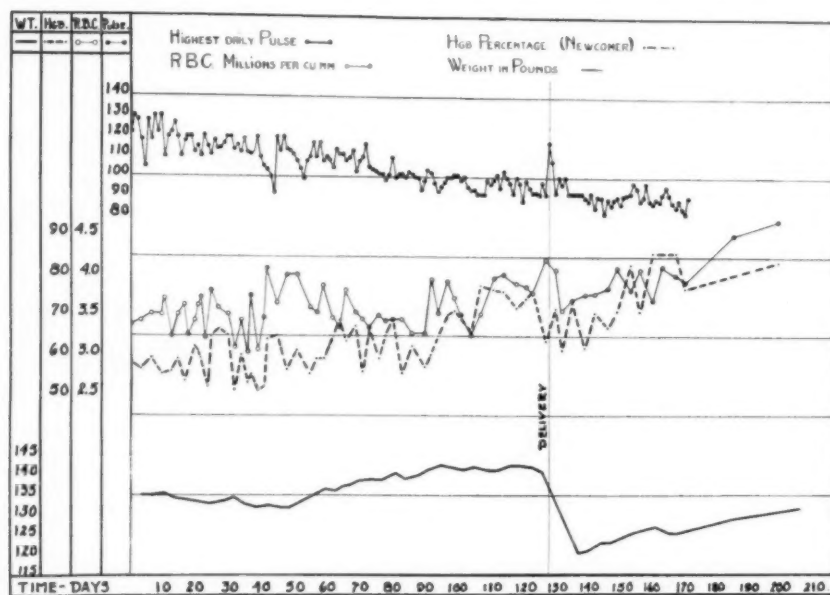
Chart 1.—This shows the highest daily pulse rate, red blood count, hemoglobin percentage (Newcomer), and the weight of the patient during her stay in the hospital.

eventually became very firm. A good part of this firmness was apparently due to scar tissue formation. There was definite shortening of the hamstring muscles and the muscles of the calves of the legs, resulting in inability to extend the knees completely and to dorsiflex the feet. After a month of treatment it was possible to apply light massage to the muscles. Perhaps if more active massage and passive motion to the legs had been used, in spite of the severe pain caused by these manipulations, less contracture would have resulted. Before delivery the patient was able to move her legs almost normally while in bed, although weakness and slight tenderness on pressure over the calves persisted. By then passive motion could be applied and the patient was able to extend the knees almost completely. The pulse remained down in the nineties. Although more or less vomiting persisted until the patient delivered, at no time during her stay in the hospital was the vomiting alarming, and the patient's weight increased to 141 pounds before delivery.

TABLE I. NEUROLOGIC EXAMINATIONS DURING AND AFTER PREGNANCY*

	5-3	5-13	5-22	6-1	6-15	6-23	7-20	8-3	8-23	9-16	10-12	10-20	11-3	12-1
1. Pain	++++	++++	++++	+++	++	+	N	N	N	N	N	N	N	N
2. Tenderness														
a. Thighs	++++	++++	++++	++++	+++	++	++	++	++	+	N	N	N	N
b. Calves	++++	++++	++++	++++	++	++	++	++	++	+	+	+	+	N
3. Weakness														
a. Hands	+	+	N	N	N	N	N	N	N	N	N	N	N	N
b. Right leg	+++	++	++	+	+	+	+	+	+	+	+	+	+	+
c. Left leg	+++	+++	+++	+++	++	++	+	+	+	+	+	+	+	+
4. Coordination														
a. Upper ext.	+	+	+	N	N	N	N	N	N	N	N	N	N	N
b. Right leg	++	++	++	++	++	++	+	+	N	N	N	N	N	N
c. Left leg	+++	+++	+++	+++	++	++	+	+	N	N	N	N	N	N
5. Vibratory sense														
a. Tibiae	+	N	N	N	N	N	N	N	N	N	N	N	N	N
b. Ankles	+	N	N	N	N	N	N	N	N	N	N	N	N	N
6. Position sense														
a. Upper ext.	N	N	N	N	N	N	N	N	N	N	N	N	N	N
b. Lower ext.	N	N	N	N	N	N	N	N	N	N	N	N	N	N
7. Knee jerks	abs.	abs.	abs.	abs.	abs.	abs.	abs.	abs.	abs.	N	abs.	abs.	N	abs.
8. Ankle jerks	abs.	abs.	abs.	abs.	abs.	abs.	abs.	abs.	abs.	abs.	abs.	abs.	abs.	abs.
9. Plantars	abs.	abs.	abs.	abs.	abs.	abs.	abs.	abs.	N	N	N	N	N	N
10. Paresthesias of hands	+	+	N	N	N	N	N	N	N	N	N	N	N	N
11. Muscle tone														
a. Calves	++++	++++	++++	++++	++++	+++	++	+	S	S	S	S	S	S
b. Thighs	++++	++++	++++	++++	++++	+++	++	+	S	S	N	N	N	N
12. Mental cond.	N	N	N	N	N	N	N	N	N	N	N	N	N	N
13. Ataxia	++	++	+	+	N	N	N	N	N	+++	++	+	+	N

*N = normal; abs. = absent; S = shortening of muscles due to fibrotic changes. Patient delivered 9-7.

The patient delivered a normal male infant weighing 7 pounds and 6 ounces on Sept. 7, 1933, after she had been in labor ten hours. The baby was delivered by low forceps after an episiotomy had been done. Gas anesthesia was used during the procedure. The patient had a normal puerperium except for the neurologic symptoms. There was no abnormal rise in pulse following the delivery and by the tenth day she was allowed out of bed.

The process of relearning to walk was rather slow. During this stage of treatment a ''walker'' was of great help. The patient was discharged from the hospital on Oct. 20, 1933, at which time she was able to walk with the help of a cane. She tended to throw her feet forward and there was slight ataxia. The red blood cell count when she left the hospital was 3.93 million and hemoglobin was 77.3 per cent.

Since leaving the hospital, the patient has continued to take the vitamin B capsules and to receive the weekly injections of concentrated liver extract. The dose of reduced iron was increased to 10 gr. three times a day, and by Nov. 17, 1933, the red blood cell count was 4.71 million and hemoglobin was 84 per cent. On that date the patient could walk without the use of a cane, although slight ataxia was present. The patient still threw the left leg forward.

SUMMARY

This patient presented the typical findings of a polyneuritis of pregnancy which had developed following pernicious vomiting and the treatment for the vomiting. The condition of the patient was critical when the vitamin B therapy was instituted. However, her condition showed definite improvement soon after the onset of therapy and she was carried to term and now has very little residue of the polyneuritis. The marked improvement of the neurologic signs and symptoms before delivery, although the nausea and vomiting persisted until after the delivery, suggests that polyneuritis of pregnancy is not the result of a toxemia but that it is due to a dietary deficiency, as suggested by Wechsler, Strauss and McDonald, and Luikart. This would indicate that vitamin B should be administered parenterally to all patients with hyperemesis gravidarum as a prophylaxis against the development of polyneuritis.

The fact that the most marked improvement of the neurologic symptoms followed the administration of the large doses of vitamin B_1 (as a concentrated extract of rice polishings) strongly indicates that relatively large quantities of the vitamin should be administered to all cases. The liver extract was administered by mouth not only because of its high vitamin B (mainly vitamin B_2) content, but also because it was thought that the active principle of the liver extract might be of some benefit to the patient. The liver extract supplied the vitamin B_2 after the Vegex was discontinued, as the extract of rice polishings has little or no vitamin B_2, although it has a very high concentration of vitamin B_1. The patient received weekly injections of liver extract because this type of therapy has been shown to be the most successful in the treatment of neurologic involvement of pernicious anemia. It is difficult to determine just what benefit was derived from the injections by this patient. However, in patients who continue to have severe vomiting, or for any other reason are unable to absorb the vitamin B complex from the gastrointestinal tract, this therapy should be of great benefit. Previous work has shown that patients having pernicious anemia[7] or pellagra[8] not responding to oral liver therapy will respond to liver extract administered parenterally. It is reasonable to assume that similar results would be obtained in cases of polyneuritis not able to absorb the vitamin B complex if liver extract or a concentrated vitamin B preparation were administered parenterally, as was suggested by Strauss and McDonald.

CONCLUSIONS

1. The value of the vitamin B complex in the treatment of polyneuritis of pregnancy is again demonstrated.

2. It seems advisable to administer vitamin B parenterally to all cases of hyperemesis gravidarum as a prophylaxis against the development of polyneuritis.

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AN IMPROVED IRRIGATING UNIT

LEONARD H. BISKIND, M.D., CLEVELAND, OHIO

CONVENTIONAL methods for the cleansing of body cavities or the application of heat thereto by irrigation are inadequate and unsatisfactory. Such methods usually require the use of a metal container or a rubber bag to which is attached rubber tubing with a suitable nozzle. The flow of water is dependent on the action of gravity, and the available pressure is limited usually to only five or six feet of water, frequently less. The temperature can be regulated only initially on filling the container. A medicated solution can be obtained only by the preliminary mixture of a definite amount of a liquid, powder, or tablet in a measured quantity of water.

The disadvantages inherent in such methods are manifold as well as obvious. To eliminate these, the possibility of producing a pressure regulator to be attached directly to the water faucet was investigated. This led to a study of tap outlet sizes and water pressures in several large cities. Sizes and shapes of faucets were found to depend more on the modernistic trend in home design than on utility. Faucet outlets were found to be oval, circular, square or hexagonal, ranging from one-half to two inches in diameter. Bevels and raised edges magnified the task of finding a universal fitting.

Water pressure in such centers as New York, Chicago, and Cleveland was found to range from 60 pounds per square inch in the residential districts of Cleveland to 100 pounds in the hotel districts of Chicago and New York. It was necessary, therefore, to include in this unit a foolproof mechanism whereby pressures could be regulated within safe limits no matter what the pressure at the inlet.

An improved irrigating unit is presented which has overcome many if not all the disadvantages of the variety of appliances now commonly in use. Its development was initiated by Messrs. R. E. Curtis and J. H. Duggan. It was brought to the attention of the author in an incomplete stage and was perfected under his guidance.

This unit consists of four simple parts as depicted in the accompanying semi-diagrammatic sketch (Fig. 1), and as shown in the accompanying photograph (Fig. 3). Part *I* is an adjustable pressure regulator which takes the place of the usual rubber bag or metal container. It consists of two parts molded together. The
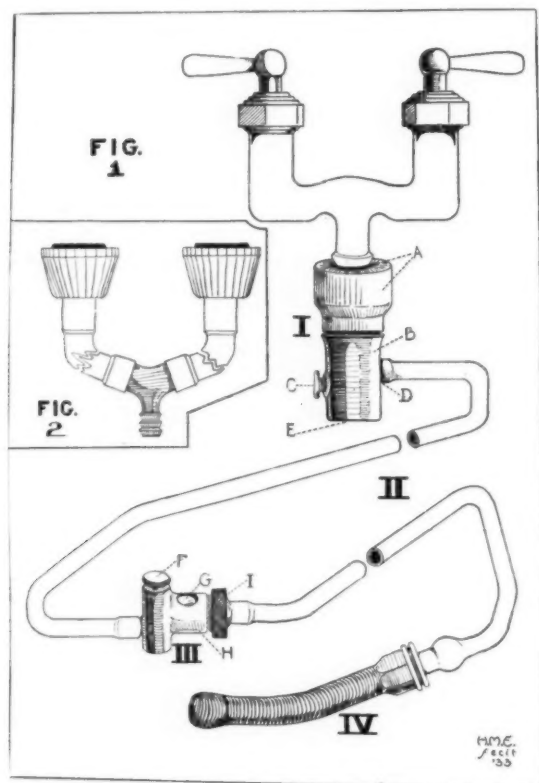
Figs. 1 and 2.

upper segment, *A*, which slips over the faucet, has an outer diameter of 1¼ inches and is composed of para rubber sufficiently elastic to fit on taps of large diameter and irregular shape without special attachments. The inlet is tapered to a depth of one inch, ending in an opening 7/16 inch in diameter; on the inside curved radius, molded in the rubber ¾ inch below the top, are two horizontal ledges ⅝ inch long. These ledges face each other and serve to provide a tighter grip on the faucet; they are particularly of help to prevent slipping on oval or irregularly shaped outlets. The upper portion of the rubber segment is hollow and is divided into six sections. These open directly into the high pressure chamber of the regulator; and the greater the line pressure the more tightly is the rubber segment compressed on the tap outlet. By this simple expedient the necessity for chains or brackets is completely eliminated.

The lower segment, *B*, of the pressure regulator consists of a chromium-plated, outer brass shell which is fitted over a hollow aluminum casting. The set screw, *C*, controls the spring tension against a diaphragm which is pressed against a brass valve seat in the casting. Manipulation of this screw produces any desired pressure at the nozzle inlet, ranging from nearly 0 to 15 pounds. The outlet, *D*, is a ribbed brass tube to which is connected the special rubber tubing, *II*. All the excess water passes through the opening, *E*, at the bottom of the metal shell. As water flows continuously through this opening its temperature may readily be determined here at any time.

As noted in the diagram and photograph, Part *II* indicates two pieces of special rubber tubing totalling seven feet in length. These are used to connect the regulator to the medicine chamber, *III*, and the latter to the nozzle, *IV*.

Part *III* has been designated the medicine chamber. It consists of a T-shaped chromium-plated metal unit combining a special monel metal spring-and-ball cut-off valve, *F*, in conjunction with a glass-lined cylindrical chamber. One-half-inch oval openings, *G*, on either side of this cylindrical portion, permit visibility of a tablet undergoing solution. The chamber, *H*, is 1 inch long and ⅝ inch in diameter. One

Fig. 3.

end is threaded to permit the removal of the cap, *I*, in order to insert the desired medication. The cap is perforated through its center and has a ½-inch tubular extension, ¼ inch in diameter. Covering the perforated end within the cap is a cylindrical mesh projection of brass wire woven twenty-four to the inch and held in place by a rubber washer. Its purpose is to prevent the escape of small undissolved particles of the tablet.

Part *IV* in the diagram is a vaginal irrigating tip. It is a slightly curved hard rubber unit 5 inches long. It consists of three portions and can be quickly dissembled for cleansing. This particular tip was chosen for use with this outfit as it provided an excellent globular spray with the range of pressures available. As noted in the accompanying photograph, one or more additional tips for pharyngeal or rectal irrigation may be used. Clinical investigation has shown that any standard stock tip, available at any drug store, can be used successfully. The choice of tips, particularly in the matter of vaginal douches, can be left to the prescribing physician.

This device has the unique advantage of being quite foolproof; any possible accident to the reducing valve will cause an immediate and complete release of pressure through the opening, *E*. Also the valve, *F*, closes instantly on release of finger pressure, and this provides an additional safeguard. Several of these units

have been in use on pressures up to one hundred pounds or more and for periods up to eight months; no mishap of any kind has occurred to the mechanism, and no accident has happened to any patient through the use of this device.

In many homes the single faucet for both hot and cold water is not available. To remedy this, a simple adapter has been constructed as shown in Fig. 2.

With the technical assistance of a pharmacologist, a series of experiments was conducted to investigate the usefulness in this unit of stock tablets of various standard medicaments as obtainable in the open market. The rate of flow through the unit at given pressures and with definite temperatures was first determined. The experimental apparatus consisted of the unit attached to the hot and cold water lines with a pressure gauge and a thermometer placed in the rubber tubing just beyond the outlet, D. In view of the fact that this unit may find its greatest use as a vaginal irrigator, the hard rubber vaginal nozzle was used in these experiments.

The pressure was determined by regulating the valve control screw, C, to a point where the globular spray coming from the vaginal nozzle measured four inches long and two inches at its greatest diameter. At a pressure of five pounds and a temperature of 102° F. (38.9° C.) (just comfortably warm to the skin of the back of the hand) the time consumed in filling successively four individual quart jars was approximately twenty seconds each. In other words, about one minute and twenty seconds was consumed in passing one gallon of water through the unit producing a spray suitable for a douche.

The rates of solution of stock tablets at a given pressure and temperature were next determined. The results are given in Table I. Assuming that there is no

TABLE I

TABLETS	SIZE IN GRAMS	TEMPERATURE	WATER* (QT.)	TIME† (IN SECONDS)	CONCENTRATION‡
1. Potassium permanganate (Brand S)	0.3	102°-104° F.	14.0	300	1:42,600
2. Acriflavine (Brand A)	0.03	104°-105° F.	2.5	60	1:83,000
3. Mercurochrome (Brand H)	0.3	104°-105° F.	3.0	70	1:11,000
4. Sodium bicarbonate (Brand N)	0.6	104° F.	3.5	80	1:53,000
5. Sodium chloride (Brand N)	1.0	103° F.	1.0	20	1:1,024
6. Alum and copper sulphate (Brand S) āā	0.6	100°-105° F.	6.0	150	1:4,650 of each
7. Mercuric chloride (Brand N)	0.5	100°-102° F.	1.5	60	1:3,072
8. Chloramine (Brand A)	0.3	100°-101° F.	1.0	25	1:3,072

*This indicates the amount of water necessary completely to dissolve tablet.
†This indicates the time necessary completely to dissolve tablet.
‡Concentration if tablet is evenly divided throughout total amount of water used.
The pressure at the outlet of the regulator was maintained at 6 pounds.

significant variation in the concentration while the first four quarts are flowing through the device, it is apparent from the rates of solution shown in this table that effective concentrations can be obtained with various stock tablets readily available on the open market, this requiring only that they be obtained in proper size and of proper compression. This phase of the problem is still under investigation.

In order to know definitely whether the concentration of the given drug varies significantly in successive quarts of solution coming from the unit, tablets of potas-

sium permanganate were dissolved in the medicine chamber as indicated in Table
II. The concentrations of potassium permanganate were determined colorimetri-
cally. When the resultant solution was not of sufficiently high concentration in

TABLE II

TABLETS	SIZE	CONCENTRATION	
1. Potassium permanganate (Brand S)	0.33 gm.	qt. No. 1	1:40,000
2. Potassium permanganate (2 tablets āā 0.33 gm.)	0.66 gm.	qt. No. 1	1:10,000
3. Potassium permanganate (3 tablets āā 0.33 gm.)	1.0 gm.	qt. No. 1	1:6,000
		qt. No. 2	1:5,000
		qt. No. 3	1:5,200
		qt. No. 4	1:7,000
4. Potassium permanganate (1 tablet)	1.0 gm.	qt. No. 1	1:5,550
		qt. No. 2	1:6,000
		qt. No. 3	1:5,500
		qt. No. 4	1:7,700

The pressure at the outlet of the regulator was maintained at 6 pounds.
The temperature of the water was maintained at 102° F. (38.9° C.).

the first quart, no further tests were made; the number of tablets was then increased
or a larger tablet used. When a satisfactory antiseptic concentration was found in
the first quart the determinations were made for the successive three also. For
vaginal and for pharyngeal irrigation, one gallon of a properly medicated solution
was considered more than ample for one treatment. It will be seen that with this
drug, suitable antiseptic concentrations can be obtained in four successive quarts
by the use of 1 gram of the substance, either as several small tablets or one large
one; from the clinical standpoint no significant variation in concentration occurs
from the first to the fourth quart. The concentrations produced with one 0.3 gm.
tablet of potassium permanganate as calculated for the whole quantity of solution
in Table I and as determined by analysis for the first quart in Table II agree
closely; this indicates that no essential change in concentration occurs even through-
out the total quantity of water necessary to dissolve the tablet. In order, therefore,
to determine whether or not a given tablet provides a suitable concentration of drug
in the resultant solution, it appears necessary only to measure the total quantity
of water required completely to dissolve the medicament in the medicine chamber;
the concentration can then be calculated directly with sufficient accuracy.

SUMMARY

An improved irrigating unit which has overcome many, if not all,
the disadvantages of the variety of appliances now in use has been
described.

Standard stock tablets of various medicaments are available on the
open market which give with this unit concentrations suitable for local
medication. Adequate concentrations are maintained in the first, and
useful portions of the fluid flowing through the unit, provided that
tablets of the proper size and compression are employed.

We are informed by various pharmaceutical houses that standard
tablets suitable for use in this unit can readily be supplied.

10616 EUCLID AVENUE

THE EXTRACT OF THYMUS IN PREGNANCY*

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(From the Department of Obstetrics, Coney Island Hospital)

IN A PREVIOUS study† of 50 parturient women, we have been able to show clinically, that the extract of thymus had a definite action on the pregnant human uterus, in situ. Before the administration of the extract over 57 per cent had slight, mild, or weak pains; 33 per cent moderate and 8 per cent pains that were characterized as strong. Following the administration of thymus extract, only 8 per cent continued to have weak, mild, or slight pains, while 52 per cent had moderate and 40 per cent strong pains.

The frequency of the uterine contractions was not materially increased, i.e., if the pains recurred every three, five, ten, fifteen, or twenty minutes this interval was not necessarily shortened, although it was in a good proportion. However, a definite rhythm was established. Pains at irregular intervals became rhythmic, with the contractions recurring at the newly established rate.

The duration of these pains was not perceptibly increased. If pains lasted thirty seconds originally, in the majority of instances they continued so, only to be increased as normal labor progressed.

It is readily seen that despite the absence of effect on the frequency and the duration of the pains, but with the appearance of a definite rhythm and slightly increased intensity, labor was materially shortened. Our multiparas delivered in seven hours, and the primiparas in 9.8 hours.

In the series of 50 cases we encountered 6 patients not in true labor. In these, pains ceased after a variable period of from four to seven hours. They were allowed to go home, to return at a later date for delivery.

These disclosures gave rise to these questions: (1) Does the thymus gland play any rôle in labor? (2) If so, to what extent and in what manner? (3) Can we initiate labor with the administration of the extract of the thymus gland?

In our present series of cases, we again had 6 patients in whom, though pains were initiated, we met with temporary failure. For the present we will eliminate these from our discussion, and confine ourselves to the detailed study of 5 patients, in whom active labor was successfully initiated and carried to satisfactory termination.

CASE 1.—A. G., twenty-six years, para iii. Admitted June 6, 1933. Previous pregnancies normal and on time. Last menstrual period Aug. 3, 1932, due May 10, 1933, an apparent postmaturity of four weeks. Position L.O.A. June 7, was given 1 c.c. of thymus extract. Within five hours pains were established and by 8:30 P.M. the cervix was approximately 2½ cm. dilated. Thereafter pains gradually diminished and then ceased entirely. On the following day, June 8, her third day in the hospital, at 12:30 P.M. she was given 2 c.c. of thymus, and at 2:30, 4:30, and 6:30, 1 c.c. At 7 P.M., pains, although mild and vague, had set in. By 2:45 A.M., June 9, the pains were quite strong, and coming every three minutes. At 9:35 A.M. the presenting part was below the spines; cervix 7 cm. dilated. At 11 A.M. the membranes were ruptured artificially, and she delivered spontaneously, a live baby weighing 11 pounds 9 ounces, and measuring 55 cm. in length, showing definitely the postmaturity. Total labor 16.05 hours.

CASE 2.—R. F., aged thirty-seven, para vii, with a history of more than 10 induced abortions, was admitted July 31, 1933, because she thought she had some labor pain. She gave a history of having 4 manual removals of the placenta, supposedly because they were adherent. There were no signs of active labor. The following day at 10:30 A.M. it was noted that the presenting part, the head, was floating, and the cervix admitted the tip of the finger. Castor oil 1½ ounces and quinine grains x, were given and the quinine repeated one hour later. No effect. At 3:15 P.M. her status was as in the morning. Another twenty-four hours were allowed to go by, in order to eliminate any question of even unrecognized labor. On Aug. 2, 1933, her third day in the hospital, at 12:40 P.M., with conditions unchanged, 2 c.c. of thymus extract were given. At 2:30 the head was at the spines and the cervix was 3 fingers or about 6 cm. dilated. At 3:45 P.M. it was fully dilated, and at 4 P.M. she spontaneously delivered a normal, 7 pound 11 ounce baby. The placenta, in this instance likewise had to be removed manually. Total labor three hours and twenty minutes.

CASE 3.—R. B., aged twenty-eight, para i, admitted Aug. 3, 1933, on advice. Weight 238. Last menstrual period Oct. 17, 1932. Due July 24, 1933. Blood pressure 160/80, some edema of the ankles, 1-plus albumin, no casts. Not in labor. At 3:05 P.M., the position was noted as L.O.A., fetal heart 140. Cervix admits tip of finger and presenting part floating. At 3:15 P.M. was given 2 c.c. of thymus and repeated at 5:15. At this time pains were moderate, about q 5 m. 8:15 1 c.c. Rectal examination at this time showed cervix to be only one finger or about 1½ cm. dilated and the pains q 10 m. At 10 P.M. another 2 c.c. of the extract was given. At 11:30 P.M. the head was just above the spines and the pains moderate. A combination of 3½ minims of thymus and 3½ minims of posterior pituitary, commonly called "thymophysin," was administered. At 6 A.M. she delivered spontaneously a live male baby, weighing 9 pounds 12 ounces. There was a first degree laceration. Bleeding moderate. Total labor 14:45 minutes.

This patient presents several interesting points. She weighed almost 100 pounds more than the average, showed symptoms of a mild toxemia and when aided by a minute dose of posterior pituitary, she progressed more satisfactorily.

CASE 4.—R. B., aged thirty-one, para ii, entered hospital Aug. 15, 1933. Previous pregnancies normal. Last period Nov. 6, 1932, due Aug. 13, 1933. Position L.O.A. Fetal heart 140. Cervix closed. Not in labor. On Aug. 16, she was given two 1 c.c. doses of thymus without effect. The following day, her second in the hospital, she was given 2 doses of 2 c.c. each of thymus and 1 of 1 c.c., the last at 7:45 P.M. By 8:30 P.M. regular labor pains had been definitely established. At 10:07 P.M. membranes ruptured and at 11:10 P.M. she spontaneously delivered a normal, living baby in good condition, weighing 6 pounds 10 ounces. Total labor 6¾ hours.

Case 5.—T. H. This is a most interesting case. A primipara, thirty-two years of age. Last period Dec. 15, 1932, due Sept. 22, 1933. She had been admitted 4 different times to the hospital prior to her delivery. She presented a picture of a mild thyrotoxicosis on her second admission, and more confirmatory signs and symptoms on her third. But each time, with the abeyance of her complaints, she would sign a release and leave. The fourth and final admission was on Sept. 11, 1933. She came in because she had not felt life for a week. On Sept. 12, 1933, it was noted that she was not in labor. The presenting part, the head, was floating, and there were no fetal movements or fetal heart heard. On September 13, her second day in the hospital, still not in labor, at 11 A.M., 2 c.c. of thymus was given and repeated at 1 P.M.; 1 c.c. was given at 3 P.M. At 1 P.M. it was noted that she had slight, irregular pains. At 8 P.M. they were regular and moderate; at 4 A.M., September 14, the cervix was 3 fingers or 4½ cm. dilated. She finally delivered, spontaneously, a dead, macerated, full-term fetus, weighing 6 pounds 10 ounces. Here too, it was necessary to give a small dose of thymophysin to overcome a secondary inertia. Total labor thirty-three hours.

From the foregoing 5 cases, we draw no conclusions, but cannot fail to note:

1. That the thymus extract did initiate pains simulating the normal, spontaneously originated uterine contractions.

2. That these culminated in satisfactory delivery.

3. That even the mildest toxemia showed an apparent deficiency in the expected action of the thymus extract.

4. That a definite method of dosage and approach is essential.

5. That lastly and perhaps most important, and this by inference only, the developing fetal thymus gland may have some definite rôle in initiating labor.

901 WASHINGTON AVENUE

THE PREVENTION OF IMPETIGO NEONATORUM BY USE OF BACTERIOPHAGE

PRELIMINARY REPORT

PAUL W. WINDER, M.D., ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University Hospital)

IMPETIGO contagiosa neonatorum in newborn infants is an annoying and occasionally a very serious problem in maternity hospitals. This condition is one from which very few maternity hospitals have been completely exempt, in spite of excellent nursery technic. It is generally assumed that the staphylococcus is the causative organism of this condition. If so, one can understand the difficulties involved in preventing the transmission of this organism, inasmuch as its normal habitat is the skin and inanimate objects.

Keeping this etiologic background in mind the logical sequence was to assume that if a substance which was nontoxic to the infant and one which was specifically inhibitory or toxic to the staphylococcus could be employed the disease might be

prevented. It was decided to apply a stock solution of staphylococcus bacteriophage to the skin of the newborn without otherwise altering nursery technic. It was further decided to apply the bacteriophage to all newborn female infants; the male infants to be used as controls.

The method of application of the bacteriophage is as follows: Immediately following delivery and after the usual oil bath the entire surface of the infant's body (including scalp) is washed with the bacteriophage. This is best done by pouring the "phage" on the infant's body and gently massaging the surface with the hands. The entire procedure lasts but a few minutes. The aim is to assure a surface film of "phage" covering the entire body. No special procedure for drying the skin is necessary, as it will be found that the slight surface moisture from the bacteriophage rapidly disappears as the result of evaporation. This so-called bacteriophage rub is repeated on the fifth day postdelivery, following the regular soap and water bath. The fifth day was chosen because by that time the infant is being handled more frequently, and because the disease occurs most often between the first and sixth days of life. The bacteriophage solution being nontoxic and sterile may be applied more often, and probably should be repeated where an epidemic is in progress. As already stated, only female infants received this treatment, the male infants being given the usual oil bath followed by daily soap and water baths.

Since this experiment was started 117 infants have been admitted to the nursery, 56 girl babies receiving the treatment and 61 boy babies receiving no treatment. In this latter group there have occurred twenty-one cases of impetigo contagiosa neonatorum, but in no instance has a girl baby had the disease.

As this experiment has been in progress only a short time, definite conclusions cannot be drawn; but the use of staphylococcus bacteriophage as a surface wash for newborn infants appears to be a preventive of impetigo neonatorum in the newborn. This preliminary report is made with the hope that this method of prevention of impetigo neonatorum may be tried and found useful elsewhere.

METHOD OF PREPARATION OF BACTERIOPHAGE

The bacteriophage is prepared by the Clinical Laboratories of the University Hospital under the supervision of Dr. R. L. Kahn according to the following method. The organism used is Gratia H strain of *Staphylococcus albus*, obtained originally from Dr. Gratia of Brussels. This strain has been found to produce a bacteriophage effective in lysing approximately 85 per cent of the strains of staphylococcus isolated from infections. The following set-up is used:

The reagents and quantities employed in the preparation of bacteriophage are: 1,000 c.c. plain beef infusion broth, P_H 7.8 to 8.0; 50 c.c. stock bacteriophage, as an incitant and 40 c.c. of a young culture (four hours) of the staphylococcus in plain broth.

1. The bacteriophage and culture are added to the broth and the mixture incubated at room temperature for twenty-four hours. It is then filtered through a Berkefeld filter (N).

2. This filtrate is reinoculated with 40 c.c. of a young culture (four-hour) of the staphylococcus in plain broth and allowed to incubate twenty-four hours at room temperature, after which it is again filtered.

3. This last step is repeated once, after which the bacteriophage is transferred to sterile bottles and kept in the ice box for use.

4. A titration test is run on all lots of bacteriophage to test its lysing potency. Ten tubes each containing 3.0 c.c. of plain broth, P_H 7.8, are placed in a rack. Three-tenths of a cubic centimeter of the bacteriophage to be tested is added to the first and ninth tubes. The ninth tube serves as a phage control. A fresh pipette is used to mix the contents of the first tube, and 0.3 c.c. is transferred to the second

tube. This is likewise mixed with a fresh pipette and 0.3 c.c. transferred to the third tube. This procedure is continued through the first eight tubes.

To the tenth tube is added one loop of a young culture of the organism for which the bacteriophage has been made, and then one loop to the eighth, seventh, etc.

The tubes are incubated at 37° C. for twenty-four hours, and at that time the titer is read. The titer is the dilution represented by the last successive tube to remain clear. That is, if the first 5 tubes are clear, the titer is 1:100,000. If the titer is 1:100,000 or more, the bacteriophage is considered sufficiently lytic for use. If the titer is below that, Step 2 is repeated and the bacteriophage again tested.

Items

American Board of Obstetrics and Gynecology

The next written examination and review of case histories of Group B applicants for certification will be held in various cities of the United States and Canada on Saturday, March 24, 1935. Case histories for review may be filed with the Secretary any time prior to this date after the approval of a candidate's credentials.

The general examination for all candidates will be held in the Atlantic City General Hospital on Monday, June 10 and Tuesday, June 11, 1935, immediately prior to the scientific session of the American Medical Association.

An unusual number of candidates is expected for this meeting, and on this account early application is advisable in order to qualify. Applications for Group B candidates must be received not later than February 23, 1935, and for Group A candidates not later than May 10, 1935.

For further information, booklets, and application blanks apply to the Secretary, Dr. Paul Titus, 1015 Highland Building, Pittsburgh, (6) Pa.

Central Association of Obstetricians and Gynecologists

At the last annual meeting of the Association held November 1, 2, and 3 in New Orleans, the following officers were elected:

Dr. Willard R. Cooke, Galveston, President
Dr. Buford G. Hamilton, Kansas City, President-Elect
Dr. Jean Paul Pratt, Detroit, Vice-President
Dr. Ralph A. Reis, Chicago, Secretary-Treasurer

The next annual meeting will be held in Omaha in October, 1935.

Society Transactions

AMERICAN GYNECOLOGICAL SOCIETY

FIFTY-NINTH ANNUAL MEETING

White Sulphur Springs, W. Va., May 21, 22, 23, 1934

The following papers were presented:

1. Emphysematous Vaginitis. Drs. Clarence B. Ingraham, and Ivan C. Hall, Denver, Colo. (See page 772, November issue.)

ABSTRACT OF DISCUSSION

DR. GEORGE GELLHORN, St. Louis, Mo.—I have seen this or a very similar condition in two sisters both of whom were under twenty-five years of age. In both cases the vagina was studded with innumerable very small cysts. Microscopic examination revealed simple cysts lined with low cylindrical epithelium. In one of these two patients the attending physician had, in the course of six months or more, punctured forty or fifty of these cysts, and in one of these open cavities, there developed later an adenocarcinoma which was located about halfway between the vaginal entrance and the cervix.

2. Syphilis of the Placenta. Dr. James R. McCord, Atlanta, Ga. (See page 743, November issue.)

ABSTRACT OF DISCUSSION

DR. JOHN R. FRASER, Montreal, Canada.—The incidence of syphilis seems to vary greatly in the different parts of this continent. Dr. J. Whitridge Williams, in a series of stillbirths, reported an incidence in the colored race of 34 per cent, and 12 per cent in the white. In our Clinic it is comparatively rare.

The importance of this work of Dr. McCord's is more apparent when we realize that as the result of imperfect or insufficient treatment, many children are being born who are apparently perfectly well, but who develop symptoms of syphilis in later months. For this reason it is of great value to know the relative value of x-ray studies of bone changes and histologic changes in the placenta.

It is difficult to construct a clear picture of the placental changes of syphilis. It is essentially a vascular disease as readily demonstrated in blood vessel injections of syphilitic placentas when the vascular tree can be shown as being widely affected in a sclerotic process, large areas will be inadequately supplied, and in others a very fragmentary circulation exists. In others where the disease is known definitely to be present, lesser changes occur. For this reason a typical picture is not present sufficiently often that one could construct a characteristic x-ray visualization of the vascular tree which would be specific. It is of value only when considered together with other data.

In considering the histologic picture, we have certain criteria which can be laid down. The close packing together of the villi with an apparent budding of the chorionic epithelium, pronounced, epithelial conglomeration with thickening of the stroma and scantiness of vascular tissue can be regarded as suggestive changes, but far from absolute evidence of syphilis.

I believe that occasionally in the vessels of the cord and about them, the infiltration and the small areas of necrosis in the mesodermic stroma might be of more value than the picture of the placenta itself.

The question too comes up as to whether evidence of syphilis can be found before the fifth month, and whether or not the disease is transmitted before this. Certainly at that time areas of degeneration begin in the placenta normally and that would make the transmission of syphilis take place much more readily. I feel that diagnosis of the placenta in the early stages of syphilis would be very difficult, whereas later there may be some changes which one could make out that would be of value.

DR. M. PIERCE RUCKER, Richmond, Va.—My experience with the examination of the placenta as a diagnostic procedure is very similar to Dr. McCord's.

His present work of correlating the histologic picture with the blood Wassermann of the mother and with the findings in the fetuses is a very valuable one. It is significant that the placenta in these syphilitic mothers was positive ten times more frequently in the group with dead babies than in the group with live babies. But the correlation is by no means perfect. There were in his series quite a few positive placentas with live babies. It is even more interesting to note that there were some 14 cases with negative placentas in which the spirochetes were found in the fetuses; and some 41 cases with negative placentas in which x-ray examination of the offspring, whether dead or alive, showed definite syphilitic changes in the bone. This brings up the question whether the spirochete can pass through a normal placenta. Another possibility, of course, is that the lesion in the placenta might be so insignificant as to be overlooked. Or again the placenta might recover from its infection after it had transmitted it to the fetus.

DR. McCORD (closing).—Replying to Dr. Rucker's question, I do not know how the organisms of syphilis get through the placenta. It is possible that they bore directly through the blood vessels or the lymphatics. There are certain changes in the umbilical cord near the placenta seen in a certain number of cases; there are an increased number of leucocytes and organisms of syphilis may be found, but they are not found with any degree of uniformity at all. I personally believe that the organisms of syphilis are present in many early abortions. I have found the organisms of syphilis in many small fetuses; in a 14 gm. fetus and in a 25 gm. fetus. I believe that, if we study enough silver-stained tissues of these early abortions, we will often find the organisms of syphilis. If a spirochete travels by the lymphatics or blood stream, it does not seem logical to me that placental syphilis does not develop until around the fifth month of pregnancy.

3. The Status of the Residual Tube Following Ectopic Pregnancy in Relation to Sterility and Further Pregnancy. Dr. Isidor C. Rubin, New York City. (See page 698, November issue.)

ABSTRACT OF DISCUSSION

DR. EDWARD A. SCHUMANN, Philadelphia, Pa.—The point which concerns us is the procedure which we shall adopt with regard to the remaining tube in ectopic pregnancy. Dr. Rubin has well emphasized that the first essential is the condition of the patient; the old dictum to get in and get out should not be lightly ignored. In such cases, or even if the case is a borderline one, if the patient is moderately traumatized by her ectopic pregnancy, I believe it is far safer to carefully scrutinize the condition of the remaining tube and to do nothing at the time but possibly perform a salpingostomy, doing a further operation at some future date. If we believe, and I do firmly believe, that the great majority of

cases of tubal pregnancy follow a healing salpingitis and that the pregnancy occurs because one tube is partially occluded, there may well in the future develop further healing of the residual tube with the possibility of future normal pregnancies. An intrauterine pregnancy does occur four times more frequently than does a subsequent ectopic pregnancy. Where the patient is not damaged I believe it well to perform any one of the operations for restoring tubal function. If the tube is damaged too much, the operation described by Dr. Norris, or the Estes operation, has in my mind a distinct value, but I believe the main point is that the first essential should be the degree of damage which the patient has suffered at the time of operation.

DR. HARVEY B. MATTHEWS, BROOKLYN, N. Y.—The first question that comes up in our clinic is what to do with the tube in which the pregnancy occurs. In the last 254 tubal insufflations by the Rubin method that we have done at the Long Island College Hospital, there were four patients who had been operated upon for ectopic pregnancy in whom the remaining tube in three cases was patent and one in which the tube was closed. These statistics do not prove anything particularly so far as the mere statistics go, but they do show that we can tell the patient definitely the condition of the other tube, if we make this test routinely. In cases where we have left the stump, doing perhaps some operation on the tube in which the ectopic has occurred, we may be able to tell the patient that even that tube is patent.

Is it dangerous to leave portions of the remaining tube, even with some kind of a plastic operation?

Since Dr. Rubin has shown that the intrauterine pregnancy is four times as apt to occur as the tubal pregnancy, would this be likely to cause more frequent ectopics? In other words, if there is a damaged opposite tube, should we do any plastic operation on the affected tube, or should we remove it entirely? Dr. Rubin's paper impresses upon us the importance of a close follow-up with insufflation tests of every single ectopic pregnancy.

I had a case about three years ago in which a Rubin test was done and on the way home the patient went into shock. She came into the Long Island College Hospital and a diagnosis was made of ruptured ectopic. At operation she was found to have had a tubal abortion. It was an ampullar pregnancy; however, there was much hemorrhage and the woman was in profound shock. This one case demonstrates that an insufflation test should never be done in the presence of pregnancy.

DR. ARTHUR H. CURTIS, CHICAGO, ILL.—At the time of operation for relief of tubal gestation, if it is desired to preserve the function of childbearing, it is well to consider the possible advantage of intraabdominal insufflation of the remaining tube. One can very easily, with a Luer syringe fitted with a glass adapter, determine the amount of pathology within the tube. It is my practice to do this almost routinely in these cases.

DR. RUBIN (closing).—In a previous publication I made it clear that insufflation is contraindicated when a period has been skipped; that is, to avoid the presence of an ectopic pregnancy as well as an intrauterine pregnancy. In my earlier experience, a patient with habitual amenorrhea aborted some four months after an insufflation and it was evident that she must have been pregnant at the time of insufflation. This case called my attention to the fact that it should not be done in women who have habitual amenorrhea, during their amenorrheic period. There is no hurry about doing an insufflation in a sterile patient. One can wait for the most favorable time and such time is, as we all know, within the first week after a regular menstrual period.

I think Dr. Curtis' point was well taken. I do intraabdominal insufflation of the remaining tube almost as a routine, and mentioned in my paper that even when the tubes are inspected it is not always possible to say whether the lumen of the tube is normally patent.

4. **Sarcoma of the Uterus.** Dr. Robert A. Kimbrough, Jr., Philadelphia. (By invitation.) (See page 723, November issue.)

ABSTRACT OF DISCUSSION

DR. CHARLES C. NORRIS, PHILADELPHIA, PA.—Sarcoma of the uterus is relatively infrequent. The infrequency of sarcomatous change in myoma is of great practical importance because of the present method of treating certain myomas by irradiation. If sarcomatous change in uterine myomas were of common occurrence the justification for irradiation would be very questionable. Even if we elected to treat a given case of sarcoma by irradiation the usual dosage employed for myoma is inadequate for the malignant tumors.

Another point which Dr. Kimbrough has brought out is that from a practical standpoint, there are two types of sarcoma, the one a highly malignant anaplastic type which exhibits rapid growth, gives early metastases and frequently recurs rapidly, despite any treatment. It is particularly prone to develop late in life, especially after the menopause. This type is generally primary and not associated, except accidentally, with myoma. They are usually rather radiosensitive and postoperative irradiation should be routinely employed.

The second type which occurs as a sarcomatous change in a myoma is usually a spindle-celled tumor. This neoplasm is of slower growth and is generally far less malignant than the primary tumors. The fact that it develops with:n the substance of a myoma itself tends to safeguard the host for a time at least. The postoperative prognosis in the spindle-celled group is usually moderately good and whereas these tumors are less radiosensitive than the primary group, I believe that postoperative irradiation will add somewhat to the ultimate five-year salvage.

The histologic diagnosis of the primary tumor is generally an easy matter. In the spindle-celled variety it is important to differentiate these from degenerating myoma. Grossly a sarcomatous change usually manifests itself as a rather smooth, homogeneous, moderately vascular, softened area which if situated near the periphery of the neoplasm can often be detected eroding into the capsule of the myoma. It is important that all myoma be sectioned freely and tissue from all suspicious areas be secured for microscopic examination. Sections should also be secured from adherent areas upon the tumor surface and from the point of amputation if a supravaginal hysterectomy has been performed. In the histologic diagnosis of the spindle-celled variety it may be worth mentioning that many myomas show extremely cellular areas in some part of their structure and that this fact alone is insufficient evidence upon which to base a diagnosis of sarcoma. The fact that there has been nearly 50 per cent recurrences in our group of these cases seems to indicate the care which has been exercised in our laboratory in this respect. A clinical fact which has been brought out by Dr. Kimbrough's study is the relative frequency of sarcoma in the aged. Any supposed myoma which continues to grow after the menopause, and especially any supposed myoma which develops after the menopause, should be viewed with suspicion. This is particularly true if irradiation is considered, for as already pointed out, the usual irradiation dosage employed for myomas is totally inadequate for a sarcoma, even if this method was selected on account of some contraindications to removal of the tumor. In this connection another practical point is that all supposed myomas which continue to grow or

produce symptoms after irradiation regardless of the age of the patient should also be studied with the thought in mind that a sarcoma may be present.

DR. HENRY T. HUTCHINS, Boston, Mass.—There are two points of especial interest. One is the statement that the histologic picture of malignancy, e'ther in sarcoma or in carcinoma, really gives us very little idea of what its clinical progress is going to be.

Another interesting question is the number of mitoses and the fact that we are now able to estimate in figures the number of mitoses and their influence on malignancy, but this really gives us very little idea of the prognosis. I feel that we ought to give very much more attention to irradiations in those cases with the large number of mitoses, that is, continued irradiation, for after all the mitotic figures represent nothing but young cells and, of course, our best results will be obtained by extensive irradiation of the young cells. I believe that in all of these cases, whether the tumor has been excised or not, irradiation should be carried out for a long time.

DR. JOSEPH BRETTAUER, New York City.—I would like to ask Dr. Kimbrough if he has any information as to how often in these cases reported from the laboratory as sarcoma, there was a preoperative suspicion, or a positive diagnosis made? I would also like to call attention to the difficulty, clinical as well as pathologic, as to a definite decision between a spindle-celled sarcoma and an ordinary fibromatous condition. While I am quite sure that in my early work a very small percentage of the large number of uteri removed were thoroughly examined microscopically, and although I have always employed supravaginal amputation, I have never met with an instance when the cervix had to be removed later for recurrence of a sarcomatous condition.

In one instance a pathologic diagnosis of sarcoma was made from a specimen of tissue close to the amputated surface. For years this patient was under close observation for a possible recurrence, until she died twelve years later of an acute lobar pneumonia.

DR. WILLIAM P. HEALY, New York City.—We do not know as a rule that we are operating upon a case of sarcoma of the uterus. It is an accidental discovery usually in the pathologic laboratory. I think, therefore, we should realize the value of postoperative irradiation which must be regarded not entirely as a therapeutic measure but as a prophylactic one and that its value will depend upon the type of pathology in the tumor. For instance, I have been in contact lately with a patient, in her late forties, who was operated upon and in whom the tumor was identified as a completely encapsulated large myoma, therefore the operating surgeon said that he could see no indication whatsoever for postoperative irradiation, as there had been complete removal of the uterus, all tumor tissue, ovaries, and tubes, and there was no evidence of any local tumor elsewhere in the pelvis. The patient now has extensive tumor recurrence, swelling of both legs, and histologic study of the tumor, which was apparently encapsulated and shows the vascular spaces running right through the tumor tissue. The histologic study would indicate that postoperative roentgen radiation might be of some value in such a case.

DR. EMIL NOVAK, Baltimore, Md.—There was much need for just such a study as Dr. Kimbrough has made in this group of cases. Clinicians have been very confused and uncertain as to the prognosis in cases of sarcoma.

As to the significance of mitoses, my impression has been that the work of Evans has been borne out in our own experience and that, speaking generally, the number of mitoses bears a definite clinical relationship to the degree of clinical malignancy of the tumor. On the other hand, I think that in most laboratories

this determination will be only approximate because the number of mitoses is influenced very decidedly by the rapidity with which the tissue is fixed. A tumor which, immediately after removal, is put into the fixing fluid will show more mitoses, other things being equal, than the one that has been allowed to lie around for an hour or two, on a cold plate in the operating room.

An important practical point is that every tumor should be carefully examined, preferably by the surgeon, before the operation is finished. All myomatous nodules should be cut into, because frequently one can form a very definite idea of the probable nature of the tumor from the gross appearance. If the cut surface presents a firm whorl-like appearance we need not be worried, but if, on the other hand, it is pulpy and raw porklike, with perhaps areas of necrosis, we should suspect sarcoma and try to establish the diagnosis with a frozen section. In such cases, especially where the tumor impinges on the cervix, one should perform a radical panhysterectomy. Another point to be borne in mind is that myomatous tumors, when found in women with bleeding, do not necessarily explain the bleeding, for, on opening the uterus, one may find an adenocarcinoma tucked away in some portion of the cavity, especially if preliminary diagnostic curettage has not been done.

DR. KIMBROUGH (closing).—Replying to Dr. Brettauer's question regarding the time of making the diagnosis, 67 per cent of our patients were diagnosed only in the laboratory. Only 3 patients were diagnosed preoperatively. The remainder were suspected and diagnosis was made at operation after removal of the tumor, or else a sarcoma of the endometrium was called carcinoma of the fundus at the time of the operation or curettage.

Dr. Hutchins asked about the pulmonary metastases. Six of the patients who died of sarcoma had pulmonary metastases.

5. **The Management of Cases of the Persistent Active Phase of Adnexoperitonitis.** Dr. Willard R. Cooke, Galveston, Texas. (By Invitation.) (See page 872.)

ABSTRACT OF DISCUSSION

DR. FREDERICK C. HOLDEN, NEW YORK CITY.—We are quite conservative at Bellevue Hospital in that we have never operated upon more than 25 per cent of the total number of gynecologic patients admitted. We have many abortion cases which give us a great deal of distress and many salpingitis cases of all different types of infection.

I am somewhat confused by the table which deals with the management of certain cases and by the charts which show the greater number of those cases as subsiding or in the process of subsiding. How can the activity of the infection be determined when the patient is operated upon one, two, or three days after admission? Our great concern is not the case of gonorrheal infection, but it is the postabortal mixed infection. The cases of gonorrheal infection do very well. The patient is given very active conservative treatment. This is divided into terms of weeks. The third week the patient is discharged and given directions how to care for herself. Skene's glands and the glands of the cervix should be cleared up. We seldom operate upon a case of this type. We have about 100 cases of this kind each year and it is remarkable how well these patients do with conservative treatment.

Constipation may cause marked symptoms as shown in a woman who had a normal temperature, was constipated for three days, was given three compound cathartic pills, followed by an elevation of temperature greater than was the original.

The temperature may also be kept up by persistent diarrhea. When the diarrhea is stopped the temperature subsides.

As to drainage, we prefer not to drain by the posterior culdesac method because it makes subsequent operation much more difficult. Occasionally the patient is so desperately ill that her load must be reduced by this method of drainage.

We have never been able to diagnose, as Dr. Cooke has, the abdominal abscess, and to open through a small incision. We are for anything that gives us a quicker turnover in our service which is always overcrowded, but our chief concern is to leave a woman symptom-free and physiologically functioning.

DR. GEORGE GELLHORN, St. Louis, Mo.—Dr. Holden has spoken of Frank Simpson's demand for a surgical abstinence of three weeks. If Simpson had insisted on a period of three months rather than three weeks, it is probable that most patients would never have needed any operation. Dr. Cooke has alluded to the tendency of ascending gonorrhea to quiet down very promptly under proper treatment. Gonorrheal pus in closed pockets or cavities is very apt to become sterile within a few weeks. In spite of alarming initial symptoms a local gonorrheal peritonitis very rarely becomes generalized and threatens life. In forty years I have seen but two deaths from that cause. In the vast majority of cases proper conservative treatment restores the patient to a fair degree of well-being. It may not be possible to achieve anatomical restitution in all cases, but at all events inflammatory adhesions are rarely as troublesome as are the postoperative adhesions which inevitably follow any partial or corrective operation.

I am quite sure that these general statements will meet with no objection. But I am not so sure that there is unanimity as to what constitutes proper conservative management in ascending gonorrhea. In my opinion that is a very complicated procedure. First of all there is the factor of time, then bodily rest, preferably in the open air. There must be attention to nutrition and regulation of bowel action. Then there is vaccine treatment, or what I prefer, foreign protein therapy.

Another indispensable factor of conservative treatment is the internal application of intense heat either in the form of diathermy or the Elliott treatment; and in some obstinate cases a mild x-ray treatment for the purpose of producing a *temporary* amenorrhea will serve to exclude for the time being the disturbing influence that menstruation exerts upon any inflammatory process in the pelvis.

Although such a really thorough conservative treatment has proved satisfactory in the great majority of cases, there will naturally always remain a residue of recalcitrant cases in which there can be no question as to the justifiability of operation, but I believe that this residue will be very much smaller than the number of cases in Dr. Cooke's series.

Regarding operation I differ from Dr. Cooke merely as to the kind of procedure to be employed. With the exception of an occasional posterior colpotomy that is forced upon us in order to drain the pus, I personally in this small number of cases that have resisted all treatment, prefer a panhysterectomy; because that gives me an opportunity to drain the entire pelvic cavity down into the vagina. The wound field can be roofed over with smooth peritoneum. I also transplant parts of the ovaries in places where they can do no harm, where they cannot degenerate cystically and give rise to discomfort. This is, of course, a very mutilating operation; and as the majority of such patients are young in years, it should be employed only as a last resort. It will, however, cure the patient permanently and not give rise to second and third or fourth laparotomies, as is usually the case after less complete operations.

In brief, then, my personal principle in ascending gonorrhea is this: try to avoid operation by every possible means; but if operation is unavoidable, operate radically.

DR. J. A. McGLINN, PHILADELPHIA, PA.—The principle of waiting in these cases of gonorrheal infection is the proper one and yet every once in a while, where a mistake has been made in the diagnosis of acute appendicitis, it is found to be simply a tube that is exuding pus. With drainage or, as I have done several times, removing the tubes and leaving the ovaries it has been amazing to see the quick convalescence in the cases where we have delayed operation. But even those few experiences would not justify us to ignore the time-honored rule of waiting because the majority of them do get well if nothing is done at all.

I am rather surprised that Dr. Cooke has given up the use of foreign proteins in the form of milk. Perhaps it is because he has fallen into the same error that many of us have and instead of giving milk injections he gives other things and you cannot get the same result from these "aristocratic" injections that you can from skimmed milk.

There are a certain number of cases upon whom an operation has to be performed, and there I am in thorough accord with the radical procedure of Dr. Gellhorn.

DR. CHARLES C. NORRIS, PHILADELPHIA, PA.—I should like to emphasize the importance of treatment of the infection in the lower genital tract. This is best accomplished after the subsidence of the symptoms of the acute pelvic peritonitis. If the infection in this area is not eradicated, subsequent exacerbations of the salpingitis are likely to result. As long as a gonococcal cervicitis exists fresh attacks in the adnexa may occur. Irregular sex habits and reinfections are also factors in exacerbations of the salpingitis in a proportion of cases.

DR. COOKE (closing).—I am very sorry that the necessity for condensing this paper into the fifteen minutes' time limit left the impression that I was very radical in these procedures. I think of myself as being just the opposite. I should have said that these 3,000 cases were not strictly consecutive; 1,000 were taken consecutively from a period during which laparotomies were performed without regard to the activity of the infection. This was done in order to get a sufficiently large number of patients who had been operated upon during the febrile stage, for comparison with cases under our present system of management. The other 2,000 cases were taken consecutively back from last December. Therefore, the figures that Dr. Holden spoke of as indicating a high percentage of interference during the active stage are simply used as our error cases from which we could build up this comparison. Since I have been head of the Service, less than 50 per cent of all uncomplicated salpingitis cases are admitted to the hospital. For a number of years none of the primary cases have been operated upon, and only 25 per cent of those who have had one recurrence after treatment. In our very high percentage of colored people, we have about 50 per cent of complications, chiefly fibromyomas; and many of these operations were filed as operations primarily for the complicating conditions. Although the figures as a whole appear radical, they do not represent the present state of affairs in our work.

Another point that I did not bring out was that in our clinical material, with its high percentage of negroes, we have a great many very advanced cases of inflammation. These negroes rarely consult us until after they have had several recurrences of active inflammation of the severe type. The figures given in the paper refer almost entirely to charity patients and not to the type of patient encountered in private practice. We have the greatest difficulty in getting these charity patients to carry out instructions for nonoperative treatment. The private patients show a very different picture. The story of recoveries would be entirely different in the intelligent group from the results in the types with which we have chiefly to deal. Again, many of our patients come from a great distance, and there is difficulty in controlling nonoperative treatment.

The study, as a whole, is one of the management of neglected and advanced cases; and not one covering the management of gonorrheal infection of the types seen among intelligent patients.

We encountered in one case a persistent diarrhea which was gradually carrying the patient off through exhaustion. This diarrhea was relieved by the drainage of a pelvic inflammation; our explanation being that it was due to enteritis of the coils of intestine forming the wall of the abscess.

Regarding colpotomy, we have found that if we leave our patients with moderate pelvic exudate alone, most of them go on to actual massive suppuration; and only in a small number has this condition become quiescent and the patient more or less well. The duration of morbidity is greatly lessened by drainage of pus. Only 17 of these patients have returned for operation after drainage. On their return for secondary laparotomies the adhesions were found to be largely disposed of by nature, if sufficient time had elapsed.

As to the duration of quiescence before operation: we started out with three weeks, gradually cut it to two weeks, and then came to the conclusion that three days were sufficient.

As to the injections, milk was used originally. We had a number of reactions which were possibly due to something wrong with the technic; and this treatment was abandoned. However, we resumed its use some years ago, and have given injections in altogether several hundred cases. We still use the milk, none of the modern preparations having been employed to any great extent. I think it probable that tabulation of the recent cases will show some evidence of favorable results.

6. Institutional Obstetrics in the United States: The Operative Incidences and Mortalities.* Dr. Rudolph W. Holmes, Chicago, Ill.

7. Iliac Lymphadenectomy With Irradiation in the Treatment of Cancer of the Cervix. Dr. Fred J. Taussig, St. Louis, Mo. (See page 650, November issue.)

ABSTRACT OF DISCUSSION

DR. GEORGE GRAY WARD, NEW YORK CITY.—This paper is of value, I believe, in focusing our attention on this unsolved problem of radium therapy in gland metastasis. Lane-Claypon in a series of 914 autopsies showed that in 406 cases the glands were involved, or 45 per cent. Bonney's figures are in the neighborhood of 40 per cent. In radiation therapy without surgery we try to accomplish the cure of gland metastasis by high voltage x-ray, either with heavy doses and few in number, or with small repeated doses, according to the technic used. We must bear in mind the results that have been obtained by some of the large cancer clinics by this method. Regaud and Lacassagne in the Paris Clinic in their reports have shown definite improvement in the last two years with their radium technic. In the Stockholm Clinic, which was slow to take up the high voltage x-ray at first, they have also reported improvement since using this method. Voltz and Healy have also seen great advantages with the high voltage method, as well as Wintz of Erlangen. While x-ray therapy as a cure for cancer in metastasized regions is still open to debate, nevertheless we have definite evidence that there is much to be gained by the x-ray treatment of gland involvement. However, I think most cancer experts will agree that surgery is preferable to irradiation of the glands, if we could avoid the primary mortality. Before we took up radium treatment we were accustomed in the Wertheim operation to do just what Dr. Taussig has advocated in the removal of these glands. We must remember also that in breast cancer

*Will appear in the current volume of the Society's transactions.

we rely on surgery more than on x-ray, and if I judged correctly this was the consensus of opinion at the meeting of the College of Surgeons in Chicago last fall.

The theory of combining radium therapy with surgical removal of the glands, as advocated by Dr. Taussig, is logical. Implanting radon seeds with removal of the glands, which was first brought out by Dr. Gellhorn, is theoretically ideal, but I think it is yet to be proved just what will be gained by that method because there are certain dangers to be considered in the implantation of the radon seeds in these locations. In the first place, there must be a definite increase in the primary mortality with this procedure. There is some danger, as Dr. Taussig said, in injury to the vessels with the radon seeds. He had one death from embolus and I understand Dr. Gellhorn had a similar death. Of course, Dr. Taussig's series is so small that when we consider the percentage of mortality as given in the paper it seems large. He had a 5½ per cent in Class II cases, and a mortality in his Class III cases of 37.5 per cent.

There is another danger from the implantation of radon seeds which has to be borne in mind. The late contraction of the postradiation connective tissue may produce serious complications such as stenosis of the ureter resulting in hydroureter and hydronephrosis with infection, severe pelvic pain, edema of the extremities from interference with the circulation, and partial or complete intestinal obstruction. These complications may be benign in origin and not necessarily due to metastatic carcinoma. They may possibly be the result of prolonged and repeated high voltage x-ray therapy as well as from excessive radium dosage. Might not the implantation of radon seeds in these vulnerable locations as advocated by Dr. Taussig result in these late contractions?

The more I work with irradiation in cancer, the more I feel that the five-year period of observation is not sufficient to properly evaluate the ultimate results of irradiation therapy. I am thinking more and more in ten-year results, as I have had many patients who have lived for five years apparently well, and yet have died of cancer a few years later. In a recent case that had been well over five years, the autopsy showed stenosis of both ureters with hydronephrosis and destruction of the kidneys. We are now trying to determine by ureteral catheterization the incidence of ureteral stricture in all Class III patients who have lived five years. I am wondering whether this danger might not be increased by implantation of radon seeds in the vicinity of the ureters.

Dr. Taussig's method is, as he states, limited in its applicability. Only the Class II cases, just beyond the borderline, with a radioresistant cell, are the ones that he selected as an operative risk. Therefore, there are very few cases that are suitable for the treatment. In those cases that are definitely in Group 3 he would not advise to have this method used.

My reaction, then, to his paper at this time is that my inclination would be to combine surgery with irradiation of the cervix, *without* the implantation of the radon seeds. This method is, of course, something that has to be proved by time. It will take more cases and a longer period of observation before we can properly evaluate the benefits of this technic.

DR. ARTHUR H. CURTIS, CHICAGO, ILL.—A year ago I presented a paper before this Society on the coincident use of vaginal surgical exposure and implantation of radium in the treatment of Stage 2 and Stage 3 cases of cervical cancer. At that time I was requested to report to you the further course in the cases discussed and also to add to my experience. I wish to tell you only that all of the patients upon whom I reported a year ago thus far present clinical cures. Other cases have been added. I do not wish now to make a further report. I congratulate Dr. Taussig on the procedure which he advocates. In the use of surgical exposure and the employment of radon seeds and radium we undoubtedly have a

means whereby we can add to the curability of the moderately advanced cases of cancer in which otherwise the prognosis is dubious. We would, of course, also employ intensive deep x-ray therapy in a majority of instances.

DR. TAUSSIG (closing).—The incidence of these cases is not quite so exceptional as I think Dr. Ward might have led you to believe. After all, Group 2 cases cover approximately 40 per cent of the cancer of the cervix cases and if we would say that 1 out of every 3 cases, or perhaps even more, are suitable for this procedure we would have approximately 15 or 20 per cent of the cases of cancer of the cervix that come to us suitable for this type of treatment.

8. The Limitations and Dangers of the Intrauterine Application of Radium in the Treatment of Carcinoma of the Body of the Uterus.

Dr. John A. Sampson, Albany, N. Y.

ABSTRACT OF DISCUSSION

DR. WILLIAM P. HEALY, NEW YORK CITY.—Dr. Sampson is entirely sound in drawing attention to the limitations that exist in the treatment of corpus tumors. Were it not for the fact that radium had come into the field in the treatment of cancer of the corpus and had shown value in clearing up cases that we had been unable to take care of surgically, we would not be discussing this subject. Experience in the various clinics in which radiation has been available in adequate amounts for treatment in cases of cancer of the corpus has demonstrated two things: first, that many of the incurable cases were apparently cured, that others were controlled for a much longer period of time than we had anticipated; and, second, that there is a distinct difference in the malignant qualities of our cases of cancer of the corpus and that unless we are prepared to identify that difference we will not be in a position to intelligently treat the cases that come under our observation.

That brings us at once to this point: these women are practically invariably beyond the menopause and when they come for consultation they have but one symptom and that is bleeding from the uterus. The only thing that complicates the picture is the diagnosis as to whether cancer is present and whether it is surgically operable. We must know also whether it comes under the highly malignant or the mildly malignant cancer cell group. If it is mildly malignant it is absolutely curable if hysterectomy is feasible, and if not feasible, it can be controlled in 75 per cent or more of the cases by radiation therapy. On the other hand if it is in the highly malignant cell group, which will make up the remaining 50 per cent of cases, it would seem to us from our experience at the Memorial Hospital that these patients may do better by radiation therapy alone. Therefore, one must know the histologic grading of the tumor. If a rather large tumor mass is found with multiple myomas one wonders at once whether to do a diagnostic curettage because of the difficulties of doing it satisfactorily and the subsequent difficulty of making any form of adequate application of radium. It is a very serious decision and I do not know how it can be decided offhand. You are then in the position of being handicapped as a surgeon and the patient is handicapped as a patient. The decision must be made as you think best. Ultimately a hysterectomy will probably be necessary. I believe that since these women are beyond the menopause and if it is felt that you cannot do a proper diagnostic curettage or apply radium satisfactorily, you can at least give adequate preoperative deep roentgen ray therapy which in these highly malignant tumors will bring about a fair amount of regression and will ultimately, I believe, prove helpful to such patients.

DR. FRANK A. PEMBERTON, Boston, Mass.—Dr. Sampson's evidence is very convincing, as is also Dr. Healy's. It leaves us, however, in somewhat of a dilemma. I suppose that time alone will tell the value of radiation *versus* operation, *versus* the combination of the two. At the Boston Free Hospital for Women we have limited the use of radium as the only treatment to cases that were poor constitutional risks, or were too far advanced locally to operate upon because we thought the application of radium would be rather blind and that it would not reach the metastases which might be present in the tubes or in the ovaries. We have done, therefore, only 23 cases with radiation treatment alone, with a five-year result of 19 per cent cures. Of course, this is a point in favor of radiation treatment.

One interesting case was a woman of sixty-five years to whom I gave radium on account of obesity. Five years later she had a recurrence in the uterus and I gave another treatment and she has since shown no recurrence in two years. Another patient aged sixty years had two doses at a six-week interval, and four months later she was having a great deal of discharge. The general condition had improved, so I did a hysterectomy and found a necrosis in the uterine cavity but no sign of cancer in the uterus, tubes or ovaries.

For three years we have applied radium in the vagina after operation as a prophylactic measure and given deep x-ray therapy. Since hearing Dr. Healy's paper last year we are more inclined to use radiation alone in cases which might be called borderline. We still feel that the good risks should have a complete hysterectomy with removal of the tubes and ovaries but we do give them preoperative radium treatment. Also postoperatively they are given high voltage x-ray and radium in the vagina. Of course, we have not been doing this long enough to present any figures.

DR. OTTO H. SCHWARZ, St. Louis, Mo.—That material can be spread into the peritoneal cavity through the fallopian tubes as in the case of cancer of the body of the uterus by the use of radium, as has been shown by Sampson, is also illustrated by a case which I wish to report. Although this does not concern cancer, it nevertheless shows, in my opinion, the dissemination of infected material from the uterus, through the tubes, to the peritoneum.

The patient concerned, who was menstruating, was seized with marked abdominal pain on the third day. Late on the same day a laparotomy was performed and a general peritonitis found. At the time of operation the right tube was slightly swollen and partially coagulated, hemorrhagic material was found coming from the fimbriated end. At operation a nonhemolytic anaerobic streptococcus was recovered. The patient died shortly after the operation and at autopsy a small eroded endometrial polyp, which was markedly congested, was found in the uterus. The same organism was recovered from the uterus at autopsy. Streptococci, in large numbers, were found in the sections made from the tip of the polyp. It is assumed, from the absence of infection in the deeper portions of the polyp and elsewhere in the uterus, that the infection was carried through the tube as a result of a retrograde menstrual flow.

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